



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|--|---|
| <p>(51) International Patent Classification ⁶ : C07D 307/79, 307/80, 307/81, 405/12, 413/12, 409/12, 407/12, 495/04, A61K 31/34 // (C07D 409/12, 333:00, 307:00) (C07D 405/12, 307:00, 261:00)</p> | <p>A1</p> | <p>(11) International Publication Number: WO 95/29907</p> <p>(43) International Publication Date: 9 November 1995 (09.11.95)</p> |
| <p>(21) International Application Number: PCT/JP95/00787</p> <p>(22) International Filing Date: 21 April 1995 (21.04.95)</p> <p>(30) Priority Data: 9408577.6 29 April 1994 (29.04.94) GB</p> <p>(71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): KAWAI, Yoshio [JP/JP]; 3-33-14, Kamikashiwada, Ushiku-shi, Ibaraki 300-12 (JP). YAMAZAKI, Hitoshi [JP/JP]; 4-3-4, Matsushiro, Tsukuba-shi, Ibaraki 305 (JP). KAYAKIRI, Natsuko [JP/JP]; 2-31-15, Umezono, Tsukuba-shi, Ibaraki 305 (JP). YOSHIHARA, Kousei [JP/JP]; 2-1-21-103, Higashi, Toride-shi, Ibaraki 302 (JP). YATABE, Takumi [JP/JP]; 4-1-1-420-302, Namiki, Tsukuba-shi, Ibaraki 305 (JP). OKU, Teruo [JP/JP]; 8-2, Midorigaoka, Tsukuba-shi, Ibaraki 305 (JP).</p> | <p>(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).</p> <p>(81) Designated States: AU, CA, CN, HU, JP, KR, MX, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> | |
| <p>(54) Title: BENZOFURAN DERIVATIVES USEFUL AS INHIBITORS OF BONE RESORPTION</p> | | |
| <p>(57) Abstract</p> <div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <p>This invention relates to a novel heterocyclic compound represented by formula (I), wherein X is O or S, Y is vinylene, or a group of formula: -NHCO-, -NHCOCH-, -NHCOCH₂-, -NHCONH- or (a) (wherein R⁶ is lower alkyl), Z is heterocyclic group which may have one or more suitable substituent(s), or aryl which may have one or more suitable substituent(s), 1 = 0, 1 and the other symbols are as defined in the specification and a pharmaceutically acceptable salt thereof which are the inhibitors of bone resorption and bone metabolism, to processes for preparation thereof, to a pharmaceutical composition comprising the same and to a method for the treatment of diseases caused by abnormal bone metabolism in human being or an animal.</p> </div> <div style="width: 30%; text-align: center;"> <p style="text-align: right;">(I)</p> </div> <div style="width: 30%; text-align: center;"> <p style="text-align: right;">(a)</p> </div> </div> | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|---------------------------------------|----|--------------------------|
| AT | Austria | GB | United Kingdom | MR | Mauritania |
| AU | Australia | GE | Georgia | MW | Malawi |
| BB | Barbados | GN | Guinea | NE | Niger |
| BE | Belgium | GR | Greece | NL | Netherlands |
| BF | Burkina Faso | HU | Hungary | NO | Norway |
| BG | Bulgaria | IE | Ireland | NZ | New Zealand |
| BJ | Benin | IT | Italy | PL | Poland |
| BR | Brazil | JP | Japan | PT | Portugal |
| BY | Belarus | KE | Kenya | RO | Romania |
| CA | Canada | KG | Kyrgyzstan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea | SD | Sudan |
| CG | Congo | KR | Republic of Korea | SE | Sweden |
| CH | Switzerland | KZ | Kazakhstan | SI | Slovenia |
| CI | Côte d'Ivoire | LI | Liechtenstein | SK | Slovakia |
| CM | Cameroon | LK | Sri Lanka | SN | Senegal |
| CN | China | LU | Luxembourg | TD | Chad |
| CS | Czechoslovakia | LV | Latvia | TG | Togo |
| CZ | Czech Republic | MC | Monaco | TJ | Tajikistan |
| DE | Germany | MD | Republic of Moldova | TT | Trinidad and Tobago |
| DK | Denmark | MG | Madagascar | UA | Ukraine |
| ES | Spain | ML | Mali | US | United States of America |
| FI | Finland | MN | Mongolia | UZ | Uzbekistan |
| FR | France | | | VN | Viet Nam |
| GA | Gabon | | | | |

- 1 -

DESCRIPTION

BENZOFURAN DERIVATIVES USEFUL AS INHIBITORS OF BONE RESORPTION

5 TECHNICAL FIELD

The present invention relates to a novel heterocyclic compound and a pharmaceutically acceptable salt thereof which are useful as a medicament.

10 BACKGROUND ART

In Japanese Patent Application Laid-open No.60-48924, No. 60-54379, etc., there are disclosed thionaphten-2-carboxylic acid derivatives and 3-phenyl-4H-1-benzopyran-4-one derivatives inhibiting bone resorption.

15

DISCLOSURE OF INVENTION

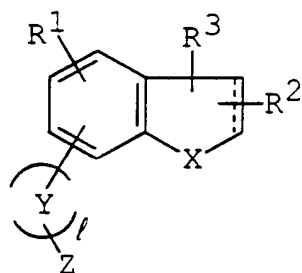
The present invention relates to a novel heterocyclic compound and a pharmaceutically acceptable salt thereof which are the inhibitors of bone resorption, the inhibitors of bone
20 metastases and useful for the prophylactic and/or therapeutic treatment of bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis); hyper-calcemia; hyperparathyroidism; Paget's bone diseases; osteolysis; hypercalcemia of malignancy with
25 or without bone metastases; rheumatoid arthritis; periodontitis; osteoarthritis; ostealgia; osteopenia; cancer cachexia; or the like in a human being or an animal.

And further, the present invention relates to processes for the preparation of the heterocyclic derivatives, to a
30 pharmaceutical composition comprising the same and to a method for the prophylactic and/or therapeutic treatment of above-mentioned diseases in a human being or an animal, and to a use of the heterocyclic derivatives and pharmaceutically acceptable salts thereof for the prophylactic and/or
35 therapeutic treatment of above-mentioned diseases in human

- 2 -

therapeutic treatment of above-mentioned diseases in human being or an animal.

The heterocyclic derivatives of this invention are new and can be represented by the following general formula (I) :



(I)

wherein

R^1 is hydrogen, lower alkyl, an acyl group, amino, acylamino, nitro, halogen or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^2 is hydrogen, lower alkyl, an acyl group, lower alkoxy, acyl(lower)alkyl, aryl, cyano, mono-(or di- or tri)-halo(lower)alkyl, lower alkylthio or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

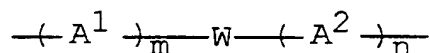
R^3 is hydrogen, lower alkyl, lower alkenyl, cyclo(lower)alkyl(lower)alkyl, halogen, an acyl group, acyl(lower)alkyl, acylamino, acylamino(lower)alkyl, acyl(lower)alkenyl, acyloxy(lower)alkyl, acyl(lower)alkylthio(lower)alkyl, amino(lower)alkyl, mono-(or di-)lower alkylamino, lower alkylthio(lower)alkyl, hydroxyimino(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkylthio(lower)alkyl, cyano(lower)alkyl, mono-(or di-)lower alkoxy(lower)alkyl which may have one or more suitable substituent(s), lower alkyl substituted with aryl which may have one or more suitable substituent(s), mono-(or di-)lower

- 3 -

alkylamino(lower)alkyl, lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), heterocyclic group which may have one or more suitable substituent(s), heterocyclicthio, heterocyclicthio(lower)alkyl, heterocyclicoxy, heterocyclicoxy(lower)alkyl, heterocyclicaminoimino-(lower)alkyl, aryl, amino or nitro,

in which R² and R³ may be linked together to form

- (1) lower alkylene which may have one or more suitable substituent(s),
- (2) lower alkenylene which may have one or more suitable substituent(s), or
- (3) a group of the formula :



[wherein A¹ and A² are each lower alkylene which may have one or more suitable substituent(s) or lower alkenylene which may have one or more suitable substituent(s),

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{W is } -\text{S}-, -\text{S}-, \text{ or } -\text{N}- \end{array} \begin{array}{c} \text{R}^5 \\ | \end{array}$$
 (wherein R⁵ is hydrogen, lower alkyl or an acyl group)

and

m and n are each integer of 0 or 1.],

X is O or S,

Y is vinylene, or a group of the formula :

-NHCO-, -NHCO₂-, -OCO-, -OCH₂-, -NHCOCO-,
 -NHCOCH=CH-, -NHCOCH₂-, -NHCONH- or -N-CO-
|
R⁶
 (wherein R⁶ is lower alkyl),

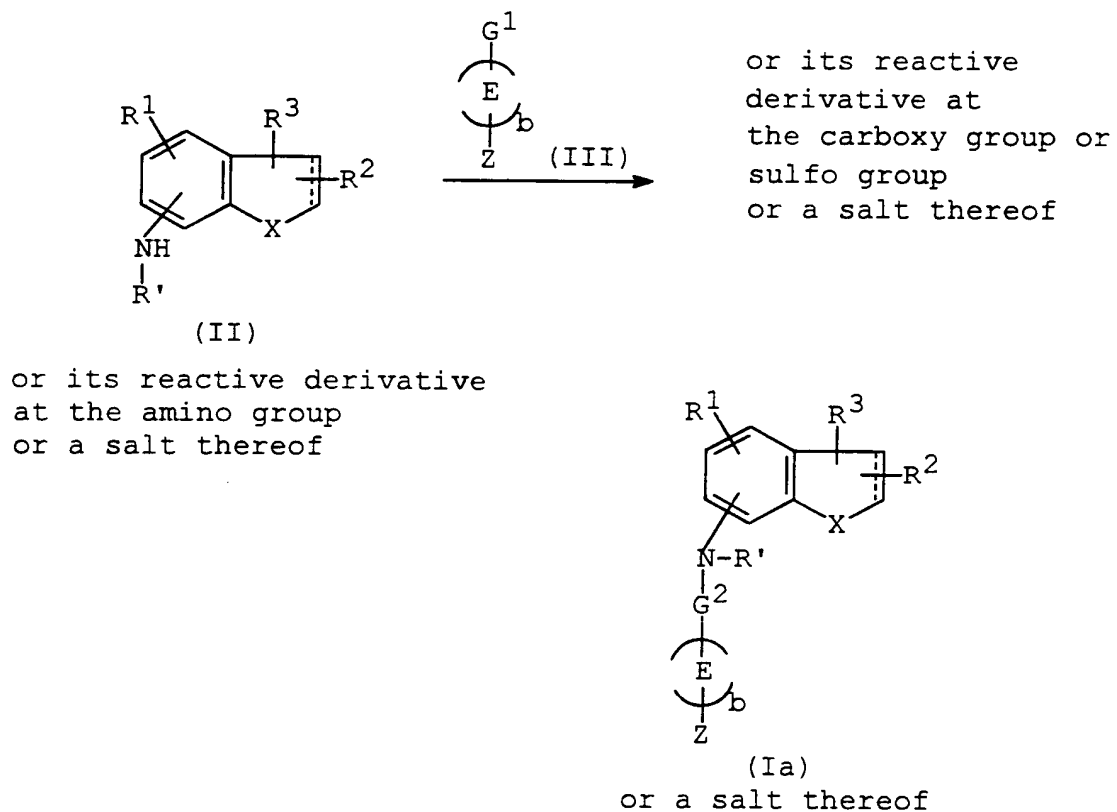
Z is heterocyclic group which may have one or more suitable substituent(s), or aryl which may have one or more suitable substituent(s),

- 4 -

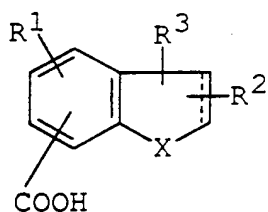
l is an integer of 0 or 1, and
 ----- is a single bond or a double bond,
 and a pharmaceutically acceptable salt thereof.

The object compound (I) or a salt thereof can be prepared by the processes as illustrated in the following reaction schemes.

Process 1

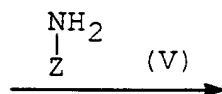


- 5 -

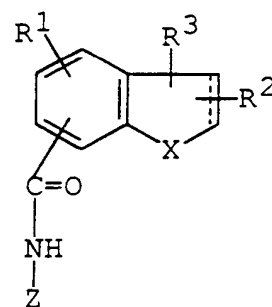
Process 2

(IV)

or its reactive derivative
at the carboxy group
or a salt thereof

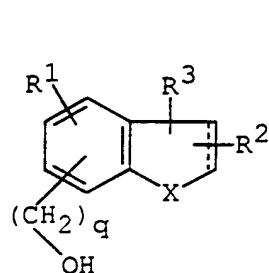


or its reactive
derivative at
the amino group
or a salt thereof



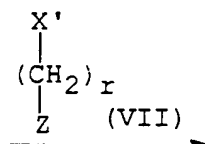
(Ib)

or a salt thereof

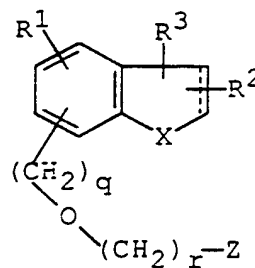
Process 3

(VI)

or its reactive derivative
at the hydroxy group
or a salt thereof



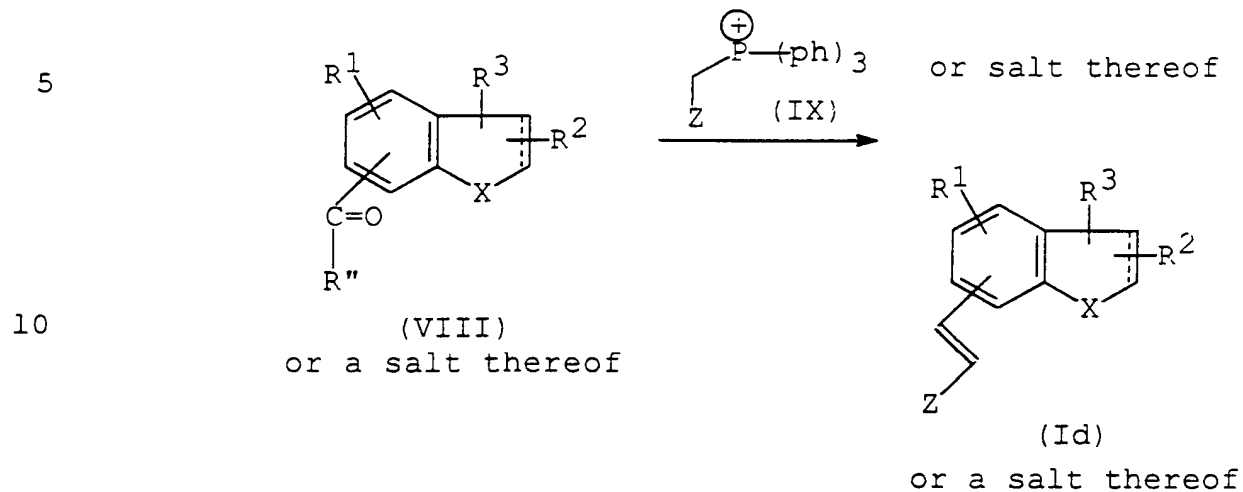
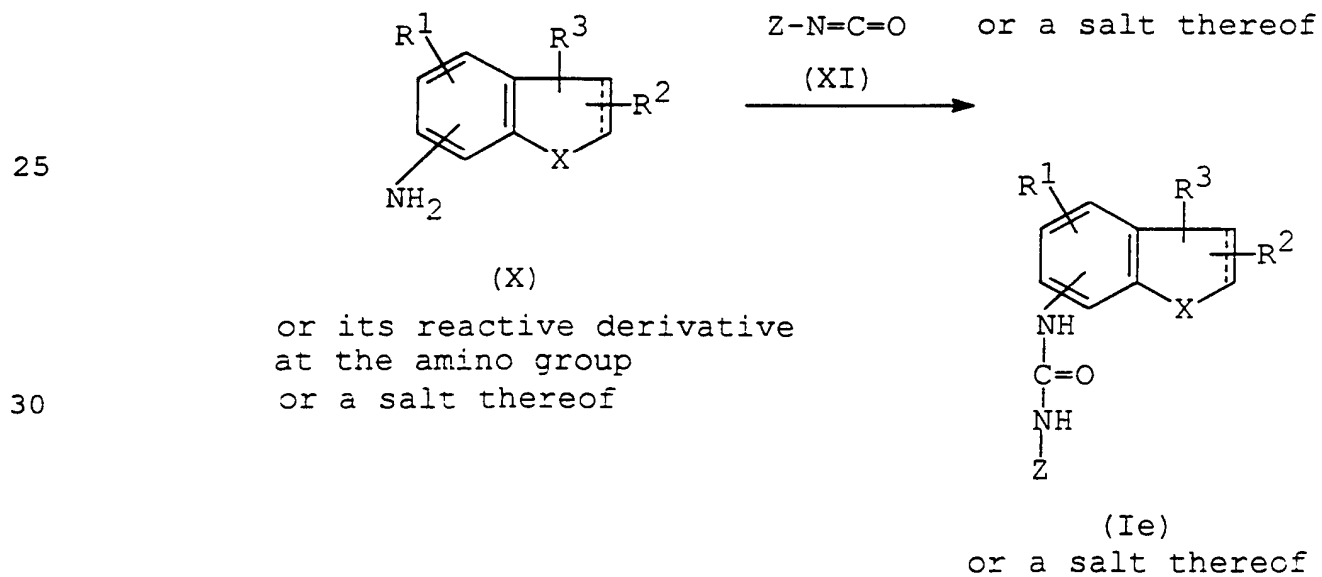
or a salt thereof



(Ic)

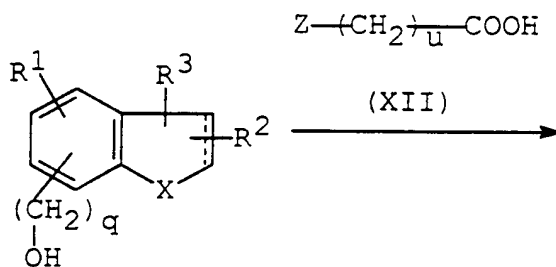
or a salt thereof

- 6 -

Process 4Process 5

35

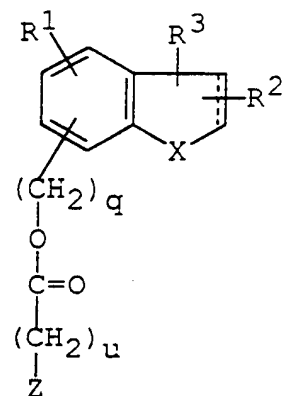
- 7 -

Process 6

(VI)

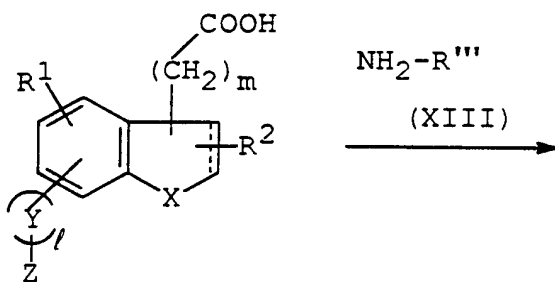
or its reactive derivative
at the hydroxy group
or a salt thereof

or its reactive
derivative at
the carboxy group
or a salt thereof



(If)

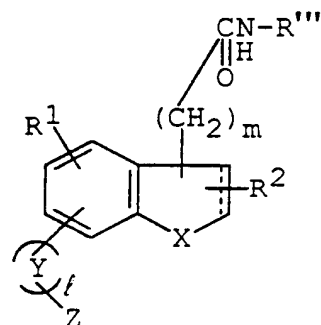
or a salt thereof

Process 7

(Ig)

or its reactive
derivative at the
carboxy group
or a salt thereof

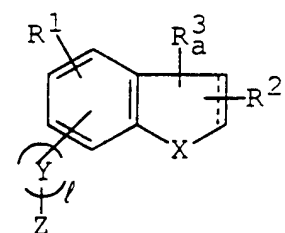
or its reactive
derivative at
the amino group
or a salt thereof



(Ih)

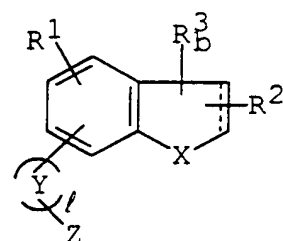
or a salt thereof

- 8 -

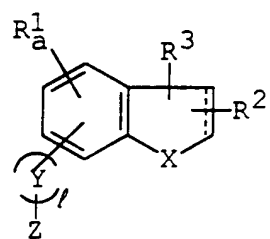
Process 8

(Ii)
or a salt thereof

Grignard reagent

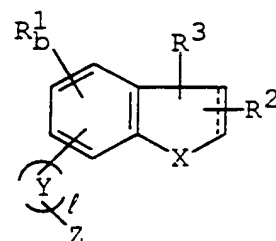


(Ij)
or a salt thereof

Process 9

(Ik)
or a salt thereof

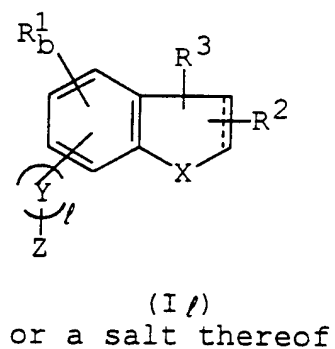
de-acylation



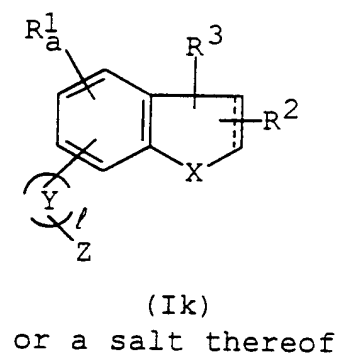
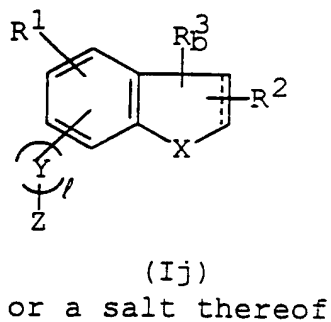
(Il)
or a salt thereof

35

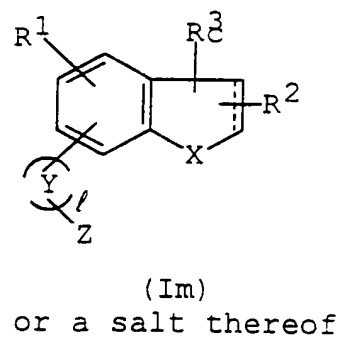
- 9 -

Process 10

acylation

Process 11

acylation



- 10 -

wherein

R^1 , R^2 , R^3 , X, Y, Z, ----- and ℓ are each as defined above,

R_a^1 is acylamino,

R_b^1 is amino,

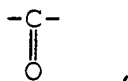
5 R_a^3 is lower alkyl substituted with oxo,

R_b^3 is hydroxy(lower)alkyl,

R_c^3 is acyloxy(lower)alkyl,

E is lower alkylene, lower alkenylene or a group of the
formula :

10



R' is hydrogen or lower alkyl,

15 R'' is leaving group,

R''' is lower alkyl, cyclo(lower)alkyl, lower alkyl
substituted with heterocyclic group which may have one
or more suitable substituent(s), lower
alkoxy(lower)alkyl, hydroxy(lower)alkyl, amino,
20 heterocyclic group, carboxy(lower)alkyl, protected
carboxy(lower)alkyl, lower alkyl substituted with aryl
which may have one or more suitable substituent(s) or
arylsulfonyl,

G^1 is $-\text{COOH}$ or $-\text{SO}_3\text{H}$,

25 G^2 is $-\text{CO}-$ or $-\text{SO}_2-$,

X' is halogen,

m is an integer of 0 to 6, and

b, r, q and u are each an integer of 0 or 1.

30 Suitable pharmaceutically acceptable salts of the object
compound (I) are conventional non-toxic salts and may include
a salt with a base or an acid addition salt such as a salt
with an inorganic base, for example, an alkali metal salt
(e.g., sodium salt, potassium salt, etc.), an alkaline earth
35 metal salt (e.g., calcium salt, magnesium salt, etc.),

- 11 -

an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

Suitable example of "one or more" may be the number of 1 to 6, in which the preferred one may be the number of 1 to 4.

Suitable "lower alkyl" and "lower alkyl moiety" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 3-pentyl, isopentyl, tert-pentyl, neopentyl, hexyl, isohexyl, and the like, preferably one having 1 to 5 carbon atom(s).

Suitable "lower alkenyl" and "lower alkenyl moiety" may include vinyl, 1-(or 2-)propenyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or 3- or 4- or 5-)hexenyl, methylvinyl, ethylvinyl, 1-(or 2- or 3-)methyl-1-(or 2-)propenyl, 1-(or 2- or 3-)ethyl-1-(or 2-)propenyl, 1-(or 2-

- 12 -

or 3- or 4-)methyl-1-(or 2- or 3-)butenyl, and the like, in which more preferable example may be (C₂-C₄)alkenyl, and the most preferred one may be methylvinyl.

Suitable "lower alkoxy" may include methoxy, ethoxy, 5 propoxy isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

Suitable "aryl" and "aryl moiety" may include phenyl, naphthyl, anthryl and the like.

Suitable "leaving group" may include acid residue and 10 the like, and suitable examples of "acid residue" may be halogen (e.g., fluorine, chlorine, bromine, iodine.), acyloxy [e.g., sulfonyloxy (e.g., phenylsulfonyloxy, tosyloxy, mesyloxy, etc.), lower alkanoyloxy (e.g., acetyloxy, propionyloxy, etc.), etc.], lower alkyl (e.g., methyl, ethyl 15 propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, neopentyl, t-pentyl, hexyl, etc.), aryl (e.g., phenyl, naphthyl, anthryl, etc.), ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.), di(lower)alkylamino (e.g., dimethylamino, 20 diethylamino, diisopropylamino, ethylmethylanino, isopropylmethylanino, ethylmethylanino, ethylpropylanino, etc.), lower alkyl(lower)alkoxyamino (e.g., methylmethoxyamino, methylethylanino, ethylmethoxyamino, ethylethoxyamino, etc.) or the like.

25 Suitable "acid residue" may include halogen (e.g., fluorine chlorine, bromine, iodine, etc.), acyloxy [e.g., sulfonyloxy (e.g., phenylsulfonyloxy, tosyloxy, mesyloxy, etc.), lower alkanoyloxy (e.g., acetyloxy, propionyloxy, etc.), etc.] and the like.

30 Suitable "lower alkylene" may include straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylimethylene, ethylethylene, ethylpropylene, and the like.

35 Suitable "lower alkenylene" may include straight or

- 13 -

branched one having 2 to 6 carbon atom(s) such as vinylene, propenylene, 1-(or 2-)butenylene, 1-(or 2- or 3-)pentenylene, 1-(or 2- or 3-)hexenylene, methylvinylene, ethylvinylene, 1-(or 2- or 3-)methylpropenylene, 1-(or 2- or 3-)ethylpropenylene, 1-(or 2- or 3- or 4-)methyl-1-(or 2-)butenylene, and the like.

Suitable "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, in which the preferred one may be cyclo(C₄-C₆)alkyl.

Suitable "halogen" and "halo" moiety may include fluorine, bromine, chlorine, and iodine.

Suitable "an acyl group" and "acyl" moiety may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl.

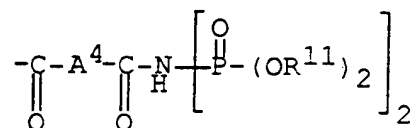
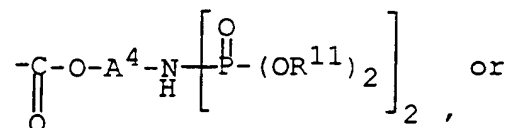
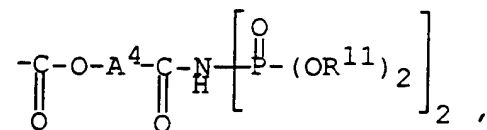
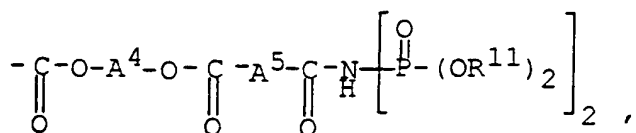
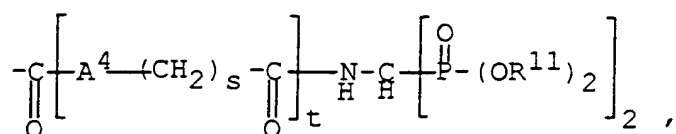
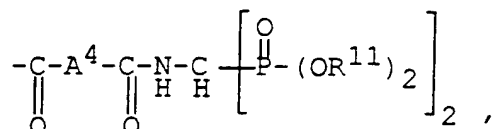
Suitable example of said acyl may be illustrated as follows :

carbamoyl; carboxy;

aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.); cyclo(lower)alkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.); protected carboxy such as commonly protected carboxy [e.g., esterified carboxy such as lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, iso-propyloxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.), etc.], or the like; lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.); lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.);

- 14 -

di-(lower)alkoxyphosphoryl (e.g., dimethoxyphosphoryl, diethoxyphosphoryl, dipropoxyphosphoryl, dibutoxyphosphoryl, dipentyloxyphosphoryl, dihexyloxyphosphoryl, etc.),
a group of the formulas :



(wherein A⁴ and A⁵ are lower alkylene, amino(lower)alkylene
or aminophenylene,

R¹¹ is lower alkyl or hydrogen and

S and t are each integer of 1 to 6, or the like);

aromatic acyl such as

- 15 -

aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);
ar(lower)alkanoyl [e.g., phenyl(lower)alkanoyl (e.g.,
phenylacetyl, phenylpropanoyl, phenylbutanoyl,
phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.),
5 naphthyl(lower)alkanoyl (e.g., naphthylacetyl,
naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];
ar(lower)alkenoyl [e.g., phenyl(lower)alkenoyl (e.g.,
phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl,
phenylpentenoyl, phenylhexenoyl, etc.),
10 naphthyl(lower)alkenoyl (e.g., naphthylpropenoyl,
naphthylbutenoyl, etc.), etc.];
ar(lower)alkoxycarbonyl [e.g., phenyl(lower)alkoxycarbonyl
(e.g. benzyloxycarbonyl, etc.), etc.];
aryloxycarbonyl (e.g., phenoxycarbonyl,
15 naphthyloxycarbonyl, etc.);
aryloxy(lower)alkanoyl (e.g., phenoxyacetyl,
phenoxypropionyl, etc.);
arylcarbamoyl (e.g., phenylcarbamoyl, etc.);
arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.);
20 arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl,
etc.); arylsulfonyl (e.g., phenylsulfonyl, p-tolylsulfonyl,
etc.); or the like.

heterocyclic acyl such as
heterocycliccarbonyl;
25 heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl,
heterocyclicpropanoyl, heterocyclicbutanoyl,
heterocyclicpentanoyl, heterocyclichexanoyl, etc.);
heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl,
heterocyclicbutenoyl, heterocyclicpentenoyl,
30 heterocyclichexenoyl, etc.); heterocyclicglyoxyloyl; or the
like; and the like.

Suitable "heterocyclic group" and "heterocyclic moiety"
may include saturated or unsaturated monocyclic or polycyclic
35 heterocyclic group containing at least one hetero-atom such

- 16 -

as an oxygen, sulfur, nitrogen atom and the like.

And, especially preferable one may be heterocyclic group such as

5 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-10 tetrazolyl, 2H-tetrazolyl, etc.), etc.;

 saturated 3 to 8-membered (more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

15 unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, phthalimidyl, etc.;

 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

25 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

 unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, 30 benzoxazolyl, benzoxadiazolyl, etc.;

 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), 35 thiadiazolyl, etc.);

- 17 -

dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example,

5 thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

10 unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, pyranyl, etc.;

15 saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s), for example, oxiranyl, oxolanyl, dioxolanyl, tetrahydrofuranyl, etc.;

20 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

25 unsaturated condensed heterocyclic group containing 1 to 4 oxygen atom(s), for example, methylenedioxyphenyl, benzodioxanyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

30 unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like,

35 and "heterocyclic group" and "heterocyclic moiety" as stated above may have one or more suitable substituent(s) such as

- 18 -

oxo; halogen (e.g., fluorine, chlorine, bromine, iodine, etc.); lower alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, etc.); aryl (e.g., phenyl, naphthyl, anthryl, etc.); lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 3-pentyl, isopentyl, tert-pentyl, neopentyl, hexyl, isohexyl, etc.); and the like.

The acyl moiety as stated above may have one to ten, same or different, suitable substituent(s) such as lower alkyl (e.g., methyl, ethyl, propyl, etc.); lower alkoxy (e.g., methoxy, ethoxy, propoxy, etc.); lower alkylthio (e.g., methylthio, ethylthio, etc.); mono-(or di-)lower alkylamino (e.g., methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, etc.); lower alkanoylamino (e.g., acetylamino, propionylamino, butyrylamino, pentanoylamino, hexanoylamino, etc.); cyclo(lower)alkylamino (e.g., cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, etc.); mono-(or di-)lower alkoxy(lower)alkylamino (e.g., methoxymethylamino, methoxyethylamino, methoxypropylamino, ethoxymethylamino, ethoxyethylamino, ethoxypropylamino, etc.); hydroxy(lower)alkylamino (e.g., hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxypentyl, hydroxyhexyl, etc.); heterocyclic(lower)alkylamino, in which "heterocyclic moiety" is aforementioned "heterocyclic" moiety; heterocyclicamino which may have one or more suitable substituent(s), in which "heterocyclic" moiety is aforementioned "heterocyclic" moiety; lower alkanoyloxy (e.g., acetyloxy, propionyloxy, butyryloxy, pentanoyloxy, hexanoyloxy, etc.); heterocyclic group, in which "heterocyclic group" is aforementioned "heterocyclic group"; di-lower alkoxy(lower)alkyl (e.g., dimethoxymethyl, dimethoxyethyl, dimethoxypropyl, diethoxymethyl,

- 19 -

diethoxyethyl, diethoxypropyl, etc.);
arylamino which may have one or more suitable substituent(s)
(e.g., phenylamino, dimethylaminophenylamino,
trifluoromethylphenylamino, trifluoromethylnaphthylamino,
5 trifluoromethylanthrlylamino, etc.);
cyano(lower)alkylamino (e.g., cyanomethylamino,
cyanoethylamino, cyanopropylamino, cyanobutylamino,
cyanopentylamino, cyanohexylamino, etc.);
arylsulfonylamino (e.g., phenylsulfonylamino
10 naphthylsulfonylamino, anthrlysulfonylamino, etc.);
protected carboxy(lower)alkylamino (e.g.,
methoxycarbonylmethylamino, methoxycarbonylethylamino,
ethoxycarbonylmethylamino, ethoxycarbonylethylamino, etc.);
tri-halo(lower)alkylamino (e.g., 2,2,2-trifluoroethylamino,
15 1-(trifluoromethyl)ethylamino,
2-(trifluoromethyl)propylamino, etc.);
cyclo(lower)alkyl (e.g., cyclopentyl, cyclohexyl, etc.);
cyclo(lower)alkenyl (e.g., cyclohexenyl, cyclohexadienyl,
etc.);
20 halogen (e.g., fluorine, chlorine, bromine, iodine, etc.);
amino, commonly protected amino as mentioned above; hydroxy;
commonly protected hydroxy as mentioned below; cyano; nitro;
carboxy; carboxy(lower)alkyl;
commonly protected carboxy as mentioned below; sulfo;
25 sulfamoyl; imino; oxo; hydrazino; amino(lower)alkyl (e.g.,
aminomethyl, aminoethyl, etc.); carbamoyloxy;
hydroxy(lower)alkyl (e.g., hydroxymethyl, 1-(or 2-
)hydroxyethyl, 1-(or 2- or 3-)hydroxypropyl, etc.), or the
like.

30 Sutable "hydroxy protective group" in the term commonly
"protected hydroxy" may include acyl as mentioned above,
phenyl(lower)alkyl which may have one or more suitable
substituent(s) (e.g., benzyl, 4-methoxybenzyl, trityl, etc.),
trisubstituted silyl [e.g., tri(lower)alkylsilyl (e.g.,
35 trimethylsilyl, t-butyldimethylsilyl, etc.), etc.],

- 20 -

tetrahydropyranyl and the like.

Suitable commonly "protected carboxy" may include esterified carboxy and the like. And suitable example of said ester may be the ones such as lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, t-pentyl ester, hexyl ester, etc.); lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g., ethynyl ester, propynyl ester, etc.);

lower alkoxy(lower)alkyl ester (e.g., methoxymethyl ester, ethoxymethyl ester, isopropoxy ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.); lower alkylthio(lower)alkyl ester (e.g., methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, isopropoxythiomethyl ester, etc.);

mono-(or di- or tri-)halo(lower)alkyl ester (e.g., 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.); lower alkanoyloxy(lower)alkyl ester (e.g., acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester,

hexanoyloxymethyl ester, 1-acetoxyethyl ester, 2-acetoxyethyl ester, 2-propionyloxyethyl ester, etc.); lower alkoxycarbonyloxy(lower)alkyl ester (e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester,

1-(or 2-)[methoxycarbonyloxy]ethyl ester, 1-(or 2-)[ethoxycarbonyloxy]ethyl ester, 1-(or 2-)[propoxycarbonyloxy]ethyl ester, 1-(or 2-)[isopropoxycarbonyloxy]ethyl ester, etc.); lower alkanesulfonyl(lower)alkyl ester (e.g., mesylmethyl ester, 2-mesyethyl ester, etc.);

lower alkoxycarbonyloxy(lower)alkyl ester (e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, t-butoxycarbonyloxymethyl ester,

1-(or 2-)methoxycarbonyloxyethyl ester,

- 21 -

1-(or 2-)ethoxycarbonyloxyethyl ester,
1-(or 2-)propoxycarbonyloxyethyl ester,
1-(or 2-)isopropoxycarbonyloxyethyl ester, etc.);
phthalidylidene(lower)alkyl ester, or
5 (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester
[e.g., (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester,
(5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-
1,3-dioxol-4-yl)ethyl ester, etc.];
ar(lower)alkyl ester, for example, phenyl(lower)alkyl ester
10 which may have one or more suitable substituent(s) (e.g.,
benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester,
phenethyl ester, trityl ester, benzhydryl ester,
bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester,
4-hydroxy-3,5-di-t-butylbenzyl ester, etc.);
15 aryl ester which may have one or more suitable substituent(s)
such as substituted or unsubstituted phenyl ester (e.g.,
phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester,
mesityl ester, cumenyl ester, 4-chlorophenyl ester,
4-methoxyphenyl ester, etc.); tri(lower)alkyl silyl ester;
20 lower alkylthioester (e.g., methylthioester, ethylthioester,
etc.) and the like.

The preferred examples of "an acyl group" may be carboxy
protected carboxy, carbamoyl, lower alkanoyl, lower
25 alkylsulfonyl, aroyl, heterocyclic carbonyl which may have
one or more suitable substituent(s), in which the more
preferred one may be carboxy, (C₁-C₄)alkoxy carbonyl,
carbamoyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkylsulfonyl, benzoyl,
carbonyl substituted with unsaturated 3 to 8-membered
30 heteromonocyclic group containing 1 to 4 nitrogen atom(s),
carbamoyl substituted with saturated 3 to 8-membered
heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1
to 3 nitrogen atom(s), carbonyl substituted with saturated 3
to 8-membered heteromonocyclic group containing 1 to 4
35 nitrogen atom(s) having (C₁-C₄)alkyl, and the most preferred

- 22 -

one may be carboxy, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, carbamoyl, acetyl, methylsulfonyl, benzoyl, morpholinocarbonyl, N-methylpiperidylcarbonyl or pyridylcarbonyl.

5

Suitable "acyl" moiety in the term of "acylamino" can be referred to aforementioned "acyl" moiety.

The preferred examples of "acylamino" may be ureido, lower alkanoylamino, lower alkoxycarbonylamino, heterocyclic carbonylamino, lower alkanoylamino(lower)alkanoylamino (e.g. acetylaminocarbonylamino, acetylaminopropionylamino, propionylaminocarbonylamino, propionylaminopropionylamino, etc.), mono-(or di-)lower alkylamino(lower)alkanoylamino (e.g., methylaminocarbonylamino, dimethylaminocarbonylamino, ethylaminocarbonylamino, diethylaminocarbonylamino, etc.), lower alkanoyloxy(lower)alkanoylamino [e.g., acetyloxyacetylaminocarbonylamino, propionyloxyacetylaminocarbonylamino, propionyloxypropionylaminocarbonylamino, etc.), heterocyclic(lower)alkanoylamino (e.g., heterocyclic-carbonylamino, heterocyclic-acetylaminocarbonylamino, heterocyclic-propionylaminocarbonylamino, etc.), lower alkoxy(lower)alkanoylamino (e.g., methoxyacetylaminocarbonylamino, ethoxyacetylaminocarbonylamino, methoxypropionylaminocarbonylamino, ethoxypropionylaminocarbonylamino, etc.), hydroxy(lower)alkanoylamino (e.g., hydroxyacetylaminocarbonylamino, hydroxypropionylaminocarbonylamino, etc.), lower alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, butylsulfonylamino, pentylsulfonylamino, hexylsulfonylamino, etc.), or mono-(or di-)lower alkoxy(lower)alkylamino(lower)-alkanoylamino (e.g., methoxymethylaminocarbonylamino, bis(methoxymethyl)aminocarbonylamino, methoxyethylaminocarbonylamino, bis(methoxyethyl)aminocarbonylamino, etc.), in which the more preferred one may be ureido, (C₁-C₄)alkanoylamino, (C₁-C₄)-alkoxycarbonylamino, carbonylamino substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 2

- 23 -

oxygen atom(s) and 1 to 3 nitrogen atom(s), (C₁-C₄)-
alkanoylamino(C₁-C₄)alkanoylamino, di(C₁-C₄)alkylamino-
(C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy(C₁-C₄)alkanoylamino,
(C₁-C₄)alkanoylamino substituted with saturated 3 to 8-
5 membered heteromonocyclic group containing 1 to 2 oxygen
atom(s) and 1 to 3 nitrogen atom(s), (C₁-C₄)alkoxy(C₁-C₄)-
alkanoylamino, hydroxy(C₁-C₄)alkanoylamino, (C₁-C₄)-
alkylsulfonylamino or bis[(C₁-C₄)alkoxy(C₁-C₄)alkyl]amino
(C₁-C₄)alkanoylamino and the most preferred one may be
10 ureido, acetylamino, t-butoxycarbonylamino,
morpholinocarbonylamino, acetylaminoacetylamino,
dimethylaminoacetylamino, acetyloxyacetylamino,
morpholinoacetylamino, methoxyacetylamino,
hydroxyacetylamino, methylsulfonylamino or
15 dimethoxyethylaminoacetylamino.

Suitable "hydroxy(lower)alkyl" may be hydroxymethyl,
1-(or 2-)hydroxyethyl, 1-hydroxy-1-methylethyl,
2-hydroxypropyl, 1-hydroxy-1-ethylethyl, 1-hydroxy-1-
20 ethylpropyl, 1-hydroxybutyl, 1-(or 2- or 3-)hydroxy-1-(or 2-
or 3-)methylpropyl, 1-(or 2- or 3- or 4-)hydroxy-1-(or 2- or
3- or 4-)methylbutyl, 1-(or 2- or 3- or 4- or 5-)hydroxy-1-
(or 2- or 3- or 4- or 5-)methylpentyl, 1-(or 2- or 3- or 4-
or 5- or 6-)hydroxy-1-(or 2- or 3- or 4- or 5- or 6-)-
25 methylhexyl, or the like.

The preferred examples of "hydroxy(lower)alkyl" may be
hydroxy(C₁-C₅)alkyl, and the most preferred one may be
hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl,
1-hydroxy-1-ethylpropyl, 1-hydroxybutyl, 2-hydroxyethyl,
30 3-hydroxy-3-methylbutyl, 1-hydroxybutyl, 2-hydroxypropyl or
2-hydroxy-2-methylpropyl.

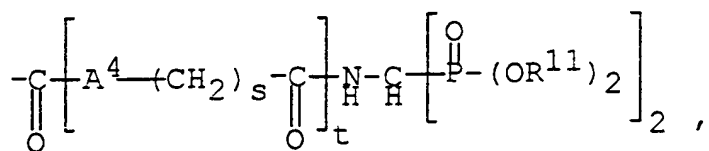
The preferred examples of "suitable substituent(s)" in
the term of "hydroxy(lower)alkyl" which may have one or more
suitable substituent(s)" may be mono-(or di- or tri)-
35 halo(lower)alkyl, protected carboxy, hydroxy, aryl,

- 24 -

cyclo(lower)alkyl or heterocyclic group, in which the preferred one may be tri-halo(C₁-C₄)alkyl, (C₁-C₄)-alkoxycarbonyl, hydroxy, phenyl, cyclo(C₃-C₆)alkyl, or unsaturated heteromonocyclic group consisting of 1 to 4 nitrogen atom(s), and the most preferred one may be trifluoromethyl, ethoxycarbonyl, hydroxy, phenyl, cyclohexyl or pyridyl.

Suitable "acyl" moiety in the term of "acyl(lower)alkyl" can be referred to aforementioned "acyl" moiety.

The preferred examples of "acyl(lower)alkyl" may be carboxy(lower)alkyl, protected carboxy(lower)alkyl, carbamoyl(lower)alkyl, lower alkanoyl(lower)alkyl, aroyl(lower)alkyl, carbonyl(lower)alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), lower alkyl having



(wherein A⁴ is lower alkylene, amino lower alkylene or aminophenylene,

R¹¹ is lower alkyl or hydrogen, and

s and t are each integer of 1 to 6),

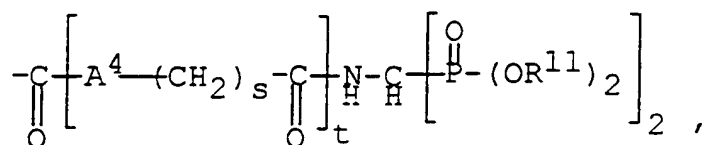
(mono- or di-)lower alkylamino)carbonyl(lower)alkyl which may have one or more suitable substituent(s) (e.g., methylaminocarbonylmethyl, dimethylaminocarbonylmethyl, methylaminocarbonylethyl, 2-dimethylaminocarbonylethyl, trifluoromethylaminocarbonylmethyl, trifluoroethylaminocarbonylmethyl, cyanomethylaminocarbonylmethyl, cyanoethylcarbonylmethyl,

- 25 -

cyanomethylcarbonylethyl, etc.),
cyclo(lower)alkylaminocarbonyl(lower)alkyl (e.g.
cyclopropylaminocarbonylmethyl,
cyclobutylaminocarbonylmethyl,
5 cyclopentylaminocarbonylmethyl,
cyclohexylaminocarbonylmethyl, etc.),
lower alkoxy(lower)alkylaminocarbonyl(lower)alkyl (e.g.,
methoxymethylaminocarbonylmethyl,
methoxyethylaminocarbonylmethyl,
10 bis(methoxymethylamino)carbonylmethyl,
bis(methoxyethylamino)carbonylmethyl, etc.), di-
(lower)alkoxyphosphoryl (e.g., dimethoxyphosphoryl,
diethoxyphosphoryl, dipropoxyphosphoryl, dibutoxyphosphoryl,
dipentyloxyphosphoryl, dihexyloxyphosphoryl, etc.),
15 mono-(or di-)hydroxy(lower)alkylaminocarbonyl(lower)alkyl
(e.g., hydroxymethylaminocarbonylmethyl,
hydroxyethylaminocarbonylmethyl,
dihydroxymethylaminocarbonylmethyl,
dihydroxyethylaminocarbonylmethyl, etc.),
20 aminocarbonyl(lower)alkyl substituted with heterocyclic group
which may have one or more suitable substituent(s) (e.g.
thiazolylaminocarbonylmethyl, pyridylaminocarbonylmethyl,
morpholinoaminomethyl, methyloxadiazolylaminocarbonylmethyl,
trifluorothiadiazolylaminocarbonylmethyl, etc.),
25 heterocyclic(lower)alkylaminocarbonyl(lower)alkyl (e.g.,
pyridylmethylaminocarbonylmethyl,
tetrahydrofuranylmethylaminocarbonylmethyl, etc.),
hydrazinocarbonyl(lower)alkyl (e.g., hydrazinocarbonylmethyl,
hydrazinocarbonylethyl, hydrazinocarbonylpropyl, etc.),
30 aminocarbonyl(lower)alkyl substituted with aryl which may
have one or more suitable substituent(s) (e.g.,
dimethylaminophenylaminocarbonylmethyl,
trifluoromethylphenylaminocarbonylmethyl, etc.),
cyano(lower)alkylaminocarbonyl(lower)alkyl (e.g.,
35 cyanomethylaminocarbonylmethyl,

- 26 -

cyanoethylaminocarbonylmethyl, cyanomethylaminocarbonylethyl, cyanoethylaminocarbonylethyl, etc.),
 arylsulfonylaminocarbonyl(lower)alkyl (e.g.,
 phenylsulfonylaminocarbonylmethyl,
 5 phenylsulfonylaminocarbonylethyl,
 phenylsulfonylaminocarbonylpropyl, etc.),
 protected carboxy(lower)alkylaminocarbonyl(lower)alkyl (e.g. methoxycarbonylmethylaminocarbonylmethyl,
 ethoxycarbonylmethylaminocarbonylmethyl,
 10 methoxycarbonylmethylaminocarbonylethyl,
 ethoxycarbonylmethylaminocarbonylethyl, etc.),
 in which the preferred one may be (C₁-C₄)alkoxycarbonyl-
 (C₁-C₄)alkyl, (C₁-C₄)alkanoyl(C₁-C₄)alkyl, carbamoyl-
 (C₁-C₄)alkyl, carboxy(C₁-C₄)alkyl, lower alkyl having



(wherein A⁴ is (C₁-C₆)alkylene, amino(C₁-C₆)alkylene or aminophenylene,

R¹¹ is (C₁-C₆)alkyl or hydrogen, and

s and t are each integer of 1 to 6),

carbonyl(C₁-C₄)alkyl substituted with heterocyclic group
 which may have 1 to 3 suitable substituent(s),
 mono-(or di-)(C₁-C₄)alkylaminocarbonyl(C₁-C₄)alkyl which may
 30 have 1 to 3 suitable substituent(s),
 cyclo(C₃-C₆)alkylaminocarbonyl(C₁-C₄)alkyl,
 (C₁-C₄)alkoxy(C₁-C₄)alkylaminocarbonyl(C₁-C₄)alkyl,
 di-(C₁-C₄)alkoxyphosphoryl(C₁-C₄)alkyl,
 mono-(or di-)hydroxy(C₁-C₄)alkylaminocarbonyl(C₁-C₄)alkyl,
 35 aminocarbonyl(C₁-C₄)alkyl substituted with heterocyclic group

- 27 -

which may have 1 to 3 suitable substituent(s),
heterocyclic(C₁-C₄)alkylaminocarbonyl(C₁-C₄)alkyl,
hydrazinocarbonyl(C₁-C₄)alkyl, aminocarbonyl(C₁-C₄)alkyl
substituted with phenyl which may have 1 to 3 suitable
5 substituent(s), cyano(C₁-C₄)alkylaminocarbonyl(C₁-C₄)alkyl,
phenylsulfonylaminocarbonyl(C₁-C₄)alkyl,
(C₁-C₄)alkoxycarbonyl(C₁-C₄)alkylaminocarbonyl(C₁-C₄)alkyl,
and the most preferred one may be carboxymethyl,
carboxyethyl, methoxycarbonyl ethyl, ethoxycarbonylmethyl,
10 ethoxycarbonyl ethyl, benzoylmethyl, carbamoylmethyl,
acetylmethyl, t-butoxycarbonylmethyl,
morpholinocarbonylmethyl, pyridylcarbonylmethyl,
chlorothienylcarbonylmethyl, pyrrolinylcarbonylmethyl,
acetyl piperazinylcarbonylmethyl,
15 phenyl piperazinylcarbonylmethyl,
methyl piperazinylcarbonylmethyl, dimethylaminocarbonylmethyl,
dimethylaminocarbonyl ethyl,
trifluoromethylmethylaminocarbonylmethyl,
cyanomethylaminocarbonylmethyl,
20 cyclopentylaminocarbonylmethyl,
methoxyethylaminocarbonylmethyl,
dimethoxyethylaminocarbonylmethyl, dimethoxyphosphorylmethyl,
diethoxyphosphorylmethyl, hydroxyethylaminocarbonylmethyl,
dihydroxyethylaminocarbonylmethyl,
25 trifluoromethylthiadiazolylaminocarbonylmethyl,
thiazolylaminocarbonylmethyl, pyridylaminocarbonylmethyl,
morpholinoaminocarbonylmethyl,
pyridyl-N-methylaminocarbonylmethyl,
methyloxadiazolylaminocarbonylmethyl,
30 pyridylmethylaminocarbonylmethyl,
tetrahydrofuranylmethylaminocarbonylmethyl,
hydrazinocarbonylmethyl,
dimethylaminophenylaminocarbonylmethyl,
trifluoromethylphenylaminocarbonylmethyl,
35 cyanomethylaminocarbonylmethyl,

- 28 -

phenylsulfonylaminocarbonylmethyl or
ethoxycarbonylmethylaminocarbonylmethyl.

The preferred examples of "mono-(or di- or tri)-
5 halo(lower)alkyl" may be
fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl,
dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl,
tribromomethyl, 1-(or 2-)fluoroethyl, 1-(or 2-)bromoethyl, 1-
(or 2-)chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, or
10 the like, in which the preferred one may be mono-(or di- or
tri-)halo(C₁-C₄)alkyl, and the most preferred one may be
difluoromethyl or trifluoromethyl.

The preferred examples of "lower alkylthio" may be
15 methylthio, ethylthio, propylthio, butylthio, pentylthio,
hexylthio, or the like, in which the preferred one may be
(C₁-C₄)alkylthio, and the most preferred one may be
methylthio.

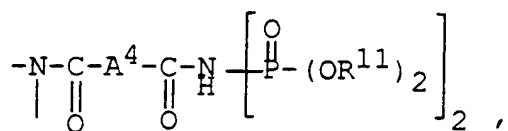
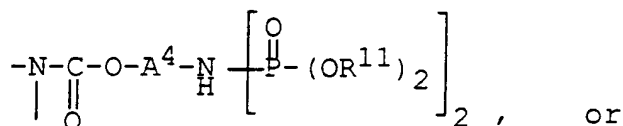
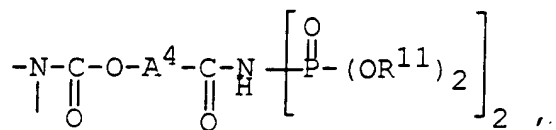
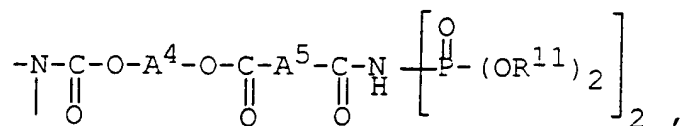
The preferred examples of
20 "cyclo(lower)alkyl(lower)alkyl" may be cyclopropylmethyl,
cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl,
cyclopropylethyl, cyclobutylethyl, cyclopentylethyl,
cyclohexylethyl, or the like, in which the preferred one may
25 be cyclo(C₃-C₆)alkyl(C₁-C₄)alkyl, and the most preferred one
may be cyclohexylmethyl.

Suitable "acylamino" moiety in the term of "acylamino-
(lower)alkyl" can be referred to aforementioned "acylamino".

30 The preferred examples of "acylamino(lower)alkyl" may be
lower alkoxycarbonylamino(lower)alkyl, lower
alkanoylamino(lower)alkyl, heterocyclic-carbonylamino-
(lower)alkyl,

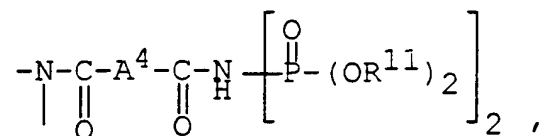
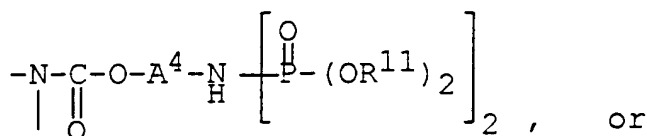
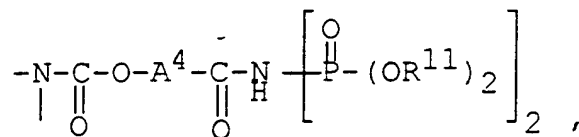
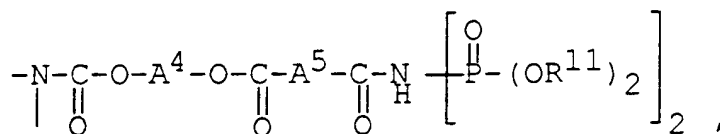
35

- 29 -



(wherein A⁴ and A⁵ are each lower alkylene,
 amino(lower)alkylene or aminophenylene, and
 R¹¹ is lower alkyl or hydrogen),
 in which the preferred one may be (C₁-C₄)alkoxycarbonylamino-
 (C₁-C₄)alkyl, (C₁-C₄)alkanoylamino(C₁-C₄)alkyl,
 carbonylamino(C₁-C₄)alkyl substituted with saturated 3 to
 8-membered heteromonocyclic group containing 1 to 2 oxygen
 atom(s) and 1 to 3 nitrogen atom(s),

- 30 -



(wherein A⁴ and A⁵ are each (C₁-C₆)alkylene, amino(C₁-C₆)-alkylene or aminophenylene, and

R¹¹ is (C₁-C₆)alkyl or hydrogen),
and the most preferred one may be t-butoxycarbonyl
aminomethyl, acetylaminomethyl or
morpholinocarbonylaminomethyl.

Suitable "acyl" moiety in the terms of "acyl(lower)-alkenyl" can be referred to aforementioned "acyl" moiety.

Suitable "(lower)alkenyl" moiety in the term of "acyl(lower)alkenyl" can be referred to aforementioned "lower alkenyl".

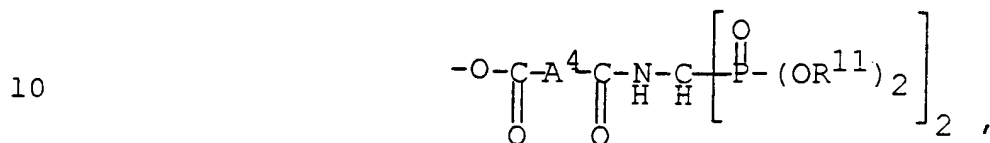
The preferred examples of "acyl(lower)alkenyl" may be protected carboxy(lower)alkenyl, in which the preferred one may be (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkenyl, and the most preferred one may be ethoxycarbonylvinyl.

Suitable "acyl" moiety in the term of

- 31 -

"acyloxy(lower)alkyl" can be referred to aforementioned "acyl" moiety.

The preferred examples of "acyloxy(lower)alkyl" may be lower alkanoyloxy(lower)alkyl, cyclo(lower)alkylcarbonyloxy(lower)alkyl, protected carboxyloxy(lower)alkyl, aroyloxy(lower)alkyl, or lower alkyl substituted with



(wherein A⁴ is lower alkylene, amino(lower)alkylene or aminophenylene, and

R¹¹ is lower alkyl or hydrogen),

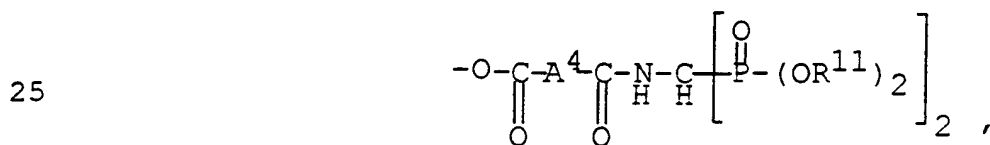
in which the preferred one may be (C₁-C₄)-

alkanoyloxy(C₁-C₄)alkyl, cyclo(C₃-C₆)-

alkylcarbonyloxy(C₁-C₄)alkyl, (C₁-C₄)-

alkoxycarbonyloxy(C₁-C₄)alkyl, benzoyloxy-

(C₁-C₄)alkyl, or lower alkyl substituted with



(wherein A⁴ is (C₁-C₆)alkylene, amino(C₁-C₆)alkylene or aminophenylene, and

R¹¹ is (C₁-C₆)alkyl or hydrogen),

and the most preferred one may be acetyloxymethyl,

1-acetyloxyethyl, cyclohexylcarbonyloxymethyl,

ethoxycarbonyloxymethyl or benzoyloxymethyl.

Suitable "acyl" moiety in the term of

- 32 -

"acyl(lower)alkylthio(lower)alkyl" can be referred to
aforementioned "acyl" moiety.

The preferred examples of
"acyl(lower)alkylthio(lower)alkyl" may be protected
5 carboxy(lower)alkylthio(lower)alkyl, in which the preferred
one may be (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkylthio(C₁-C₄)alkyl,
and the most preferred one may be
ethoxycarbonylmethylthiomethyl.

10 The preferred examples of "amino(lower)alkyl" may be
amino(C₁-C₄)alkyl, in which the most preferred one may be
aminomethyl.

The preferred examples of "mono-(or di-)lower
alkylamino" may be methylamino, dimethylamino, ethylamino,
15 diethylamino, propylamino, dipropylamino, butylamino,
dibutylamino, pentylamino, dipentylamino, hexylamino,
dihexylamino, or the like, in which the preferred one may be
mono-(or di-)(C₁-C₄)alkylamino, and the most preferred one
may be methylamino, dimethylamino or diethylamino.

20 The preferred examples of "lower alkylthio(lower)alkyl"
may be methylthiomethyl, methylthioethyl, methylthiopropyl,
methylthiobutyl, ethylthiomethyl, ethylthioethyl,
ethylthiopropyl, propylthiomethyl, propylthioethyl,
25 propylthiopropyl, or the like, in which the preferred one may
be (C₁-C₄)alkylthio(C₁-C₄)alkyl, and the most preferred one
may be methylthiomethyl.

The preferred examples of "hydroxyimino(lower)alkyl
30 which may have one or more suitable substituent(s)" may be
hydroxyiminomethyl, 1-hydroxyiminoethyl, hydroxyimino-1-
methylethyl, hydroxyimino-1-methylpropyl, hydroxyimino-1-
methylpropyl, hydroxyimino-1-amino-methyl, 2-hydroxyimino-2-
amino-ethyl, hydroxyimino-1-aminopropyl, or the like, in
35 which the preferred one may be hydroxyimino(C₁-C₄)alkyl which

- 33 -

may have amino, and the most preferred one may be 1-hydroxyiminoethyl or 2-hydroxyimino-2-aminoethyl.

The preferred examples of

5 "hydroxy(lower)alkylthio(lower)alkyl" may be hydroxymethylthiomethyl, 2-hydroxymethylthioethyl, 2-hydroxymethylthiopropyl, 4-hydroxymethylthiobutyl, 5-hydroxymethylthiopentyl, hydroxymethylthiohexyl, (2-hydroxyethyl)thiomethyl, 2-(1-hydroxyethyl)thioethyl,
10 (1- or 2-hydroxyethyl)thiopropyl, (1- or 2-hydroxyethyl)-thiobutyl, (1- or 2-hydroxyethyl)thiopentyl, (1- or 2-hydroxyethyl)thiohexyl, or the like, in which the preferred one may be hydroxy(C₁-C₄)alkylthio(C₁-C₄)alkyl, and the most preferred one may be (2-hydroxyethyl)thiomethyl.

15

The preferred examples of "cyano(lower)alkyl" may be cyanomethyl, 1-(or 2-)cyanoethyl, 1-(or 2- or 3-)cyanopropyl, 1-(or 2- or 3- or 4-)cyanobutyl, 1-(or 2- or 3- or 4- or 5-)
20)cyanopentyl, 1-(or 2- or 3- or 4- or 5- or 6-)cyanoethyl, or the like, in which the preferred one may be cyano(C₁-C₄)-alkyl, and the most preferred one may be cyanomethyl or 2-cyanoethyl.

Suitable "mono-(or di-)lower alkoxy(lower)alkyl" may be
25 methoxymethyl, methoxyethyl, dimethoxymethyl, dimethoxyethyl, ethoxymethyl, ethoxyethyl, diethoxymethyl, diethoxyethyl, propoxymethyl, propoxyethyl, propoxypropyl, dipropoxymethyl, dipropoxyethyl, dipropoxypropyl, or the like, in which the preferred one may be mono-(or di-)(C₁-C₄)alkoxy(C₁-C₄)alkyl,
30 and the most preferred one may be methoxymethyl, 2-methoxyethyl or 3-diethoxypropyl.

The preferred examples of "mono-(or di-)lower alkoxy(lower)alkyl which may have one or more suitable
substituent(s)" may be (C₁-C₄)alkoxy(C₁-C₄)alkyl or
35 tri-halo(C₁-C₄)alkyl(C₁-C₄)alkoxy(C₁-C₄)alkyl, and

- 34 -

the most preferred one may be methoxymethyl, 2-methoxyethyl, 3-diethoxypropyl or trifluoromethylmethoxymethyl.

Suitable "lower alkyl substituted with aryl" may be
5 benzyl, phenethyl, 2-phenylpropyl, naphthylmethyl, naphthylethyl, anthrylmethyl, 1-anthrylethyl, or the like, in which the more preferred one may be phenyl(C₁-C₄)alkyl, naphthyl(C₁-C₄)alkyl or anthryl(C₁-C₄)alkyl, and the most preferred one may be benzyl.

10 The preferred examples of "lower alkyl substituted with aryl which may have one or more suitable substituent(s)" may be the one which may have 1 to 3 nitro or cyano, such as phenyl(C₁-C₄)alkyl, nitrophenyl(C₁-C₄)alkyl or cyanophenyl(C₁-C₄)alkyl, in which the most preferred one may
15 be benzyl, 4-nitrobenzyl or 3-cyanobenzyl.

The preferred examples of "mono-(or di-)lower alkylamino(lower)alkyl" may be mono-(or di-)(C₁-C₄)alkylamino(C₁-C₄)alkyl, in which the more preferred one
20 may be dimethylaminomethyl.

Suitable "heterocyclic group" moiety in the term of "lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s)" can be referred to
25 aforementioned "heterocyclic group".

The preferred examples of "lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s)" may be imidazolyl(lower)alkyl, pyridyl(lower)alkyl, morpholino(lower)alkyl, pyrrolidinyl(lower)alkyl, tetrazolyl(lower)alkyl, oxiranyl(lower)alkyl, lower alkyl substituted with methylenedioxyphenyl having halogen, lower alkyl substituted with piperazine having (lower)alkyl, lower alkyl substituted with oxadiazole having (lower)alkyl, in which the more
30 preferred one may be imidazolyl(C₁-C₄)alkyl, pyridyl(C₁-C₄)-
35

- 35 -

alkyl, morpholino(C₁-C₄)alkyl, pyrrolidinyl(C₁-C₄)alkyl, tetrazolyl(C₁-C₄)alkyl, oxiranyl(C₁-C₄)alkyl, (C₁-C₄)alkyl substituted with methylenedioxyphenyl having halogen, (C₁-C₄)alkyl substituted with piperazine having (C₁-C₄)alkyl, 5 (C₁-C₄)alkyl substituted with oxadiazole having (C₁-C₆)-alkyl, and the most preferred one may be imidazolylmethyl, pyridylmethyl, 3-pyridylpropyl, morpholinomethyl, 2-morpholinoethyl, 2-pyrrolidinylethyl, tetrazolylmethyl, oxiranylmethyl, chloromethylenedioxyphenylmethyl, 10 N-methylpiperazinylpropyl, 5-methyloxadiazolylmethyl.

Suitable "heterocyclic group" moiety in the term of "heterocyclic group which may have one or more suitable substituent(s)" can be referred to aforementioned 15 "heterocyclic group".

The preferred examples of "heterocyclic group which may have one or more suitable substituent(s)", may be pyridyl which may have 1 to 3 substituent(s) selected from the group consisting of halogen and lower alkyl, thiazolyl which may 20 have 1 to 3 lower alkanoylamino, benzothienyl which may have 1 to 3 halogen, indolyl which may have 1 to 3 substituent(s) selected from the group consisting of halogen and lower alkyl, oxazolyl which may have 1 to 3 lower alkyl, pyranyl which may have 1 to 3 substituent(s) selected from the group 25 consisting of lower alkyl and oxo, pyrrolyl which may have 1 to 3 lower alkyl, phthalimido which may have nitro, phthalimidine which may have nitro, piperidyl which may have 1 to 3 lower alkyl.

30 Suitable "heterocyclic" moiety in the term of "heterocyclicthio(lower)alkyl" can be referred to aforementioned to "heterocyclic group".

The preferred examples of "heterocyclicthio(lower)alkyl" may be imidazolylthio(lower)alkyl, pyridylthio(lower)alkyl or 35 benzimidazolylthio(lower)alkyl, in which the preferred one

- 36 -

may be imidazolylthio(C₁-C₄)alkyl or benzimidazolyl(C₁-C₄)-alkyl, and the most preferred one may be imidazolylthiomethyl or benzimidazolylmethyl.

5 Suitable "heterocyclic" moiety in the term of "heterocyclicthio" can be referred to aforementioned "heterocyclic group".

 The preferred examples of "heterocyclicthio" may be pyridylthio.

10

 Suitable "heterocyclic" moiety in the term of "heterocyclic oxy" can be referred to aforementioned "heterocyclic group".

 The preferred examples of "heterocyclic oxy" may be
15 pyridyloxy.

 Suitable "heterocyclic" moiety in the term of "heterocyclic oxy(lower)alkyl" can be referred to aforementioned "heterocyclic group".

20 The preferred examples of "heterocyclic oxy(lower)alkyl" may be pyridyloxy(lower)alkyl, in which the more preferred one may be pyridyloxy(C₁-C₄)alkyl, and the most preferred one may be pyridyloxymethyl.

25 Suitable "heterocyclic" moiety in the term of "heterocyclic aminoimino(lower)alkyl" can be referred to aforementioned "heterocyclic group".

 The preferred examples of "heterocyclic aminoimino(lower)alkyl" may be aminoimino(lower)alkyl
30 substituted with unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), in which the more preferred one may be pyridylaminoimino(C₁-C₄)alkyl, and the most preferred one may be 2-pyridylaminoiminopropyl.

35 The preferred examples of "suitable substituent(s)" in

- 37 -

the terms of "lower alkylene which may have one or more suitable substituent(s)" and "lower alkenylene which may have one or more suitable substituent(s)" may be lower alkyl, hydroxy, oxo, or the like, in which the preferred one may be (C₁-C₄)alkyl, hydroxy or oxo, and the most preferred one may be methyl, hydroxy or oxo.

The preferred examples of "suitable substituent(s)" in the terms of "aryl which may have one or more suitable substituent(s)" may be halogen, lower alkyl, nitro, lower alkoxy, an acyl group, cyclo(lower)alkyl, mono-(or di- or tri-)halo(lower)alkyl, acylamino, aryl, amino, mono-(or di-)lower alkylamino, aryloxy, acyl(lower)alkyl, hydroxy, hydroxy(lower)alkyl which may have one or more suitable substituent(s), heterocyclic group which may have one or more suitable substituent(s), mono-(or di-)lower alkylamino(lower)alkyl or acyl(lower)alkyl.

The preferred examples of "mono-(or di-)lower alkylamino(lower)alkyl" may be mono-(or di-)(C₁-C₄)alkylamino(C₁-C₄)alkyl, in which the preferred one may be di(C₁-C₄)alkylamino(C₁-C₄)alkyl, and the most preferred one may be dimethylaminomethyl.

Suitable "acyl" moiety in the term of "acyl(lower)alkoxy" can be referred to aforementioned "acyl" moiety.

The preferred examples of "acyl(lower)alkoxy" may be protected carboxy(lower)alkoxy, in which the more preferred one may be (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkoxy, and the most preferred one may be ethoxycarbonylmethoxy.

The preferred examples of "suitable substituent(s)" in the term of "naphthyl which may have one or more suitable substituent(s)" may be lower alkoxy, in which the more

- 38 -

preferred one may be (C₁-C₄)alkoxy, and the most preferred one may be methoxy.

Suitable "acyl" moiety in the term of
5 "acyl(lower)alkenyl" can be referred to aforementioned "acyl" moiety.

Suitable "(lower)alkenyl" moiety in the term of
"acyl(lower)alkenyl" can be referred to aforementioned "lower alkenyl".

10 The preferred examples of "acyl(lower)alkenyl" may be protected carboxy(C₂-C₆)alkenyl, in which the more preferred one may be lower alkoxycarbonyl(C₂-C₄)alkenyl, and the most preferred one may be ethoxycarbonylvinyl.

15 The preferred examples of "aryloxy" may be phenoxy, naphthyloxy, anthryloxy, or the like, in which the most preferred one may be phenoxy.

The preferred examples of "aryl(lower)alkoxy" may be
20 phenyl(C₁-C₆)alkoxy, naphthyl(C₁-C₆)alkoxy, anthryl(C₁-C₆)-alkoxy, or the like, in which the preferred one may be phenyl(C₁-C₄)alkoxy, and the most preferred one may be phenylmethoxy.

25

The processes for preparing the object compound (I) of the present invention are explained in detail in the following.

30 Process 1

The compound (Ia) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or sulfo group or a
35 salt thereof.

- 39 -

Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (II) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative of the compound (III) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorus acid, sulfurous acid, thiosulfuric acid, alkanesulfuric acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2^+N=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-

- 40 -

pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g., sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

Process 2

The compound (Ib) or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivative at the carboxy group or a salt thereof with the compound (V) or its reactive derivative at the amino group or a salt thereof.

This reaction can be carried out in a similar manner to that of the aforementioned Process 1, and therefore the

- 41 -

reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 1.

5 Process 3

The compound (Ic) or a salt thereof can be prepared by reacting the compound (VI) or its reactive derivative at the hydroxy group or a salt thereof with the compound (VII) or a salt thereof.

10 This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the
15 reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an acid including Lewis acid.

20 Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, zinc halide (e.g., zinc chloride,
25 zinc bromide, etc.), etc.] and the like.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.),
30 an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal
35 hydride (e.g., sodium hydride, etc.), alkali metal

- 42 -

(lower)alkoxide (e.g. sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

5 When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

Process 4

10 The compound (Id) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the compound (IX) or a salt thereof to Wittig Reaction.

15 This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, tetrahydrofuran, toluene, methylene chloride, ethylene-dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

20 The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

25 The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal
30 hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline,
35 methyllitium, n-butyllitium, phenyllitium,

- 43 -

1,5-diazabicyclo[4.3.0]non-5-ene, or the like.

When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

5 Process 5

The compound (Ie) or a salt thereof can be prepared by reacting the compound (X) or its reactive derivative at the amino group or a salt thereof with the compound (XI) or a salt thereof.

10 This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the
15 reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an acid including Lewis acid.

20 Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, zinc halide (e.g., zinc chloride,
25 zinc bromide, etc.), etc.] and the like.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.),
30 an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal
35 hydride (e.g., sodium hydride, etc.), alkali metal

- 44 -

(lower)alkoxide (e.g., sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

5 When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

Process 6

10 The compound (If) or a salt thereof can be prepared by reacting the compound (VI) or its reactive derivative at the hydroxy group or a salt thereof with the compound (XII) or its reactive derivative at the carboxy group or a salt thereof.

15 Suitable reactive derivative at the hydroxy group of the compound (VI) may include halide, sulfonate, sulfate, diazo compound, and the like.

20 Suitable reactive derivative at the carboxy group of the compound (XII) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorus acid, sulfurous acid, thiosulfuric acid, alkanesulfuric acid (e.g.,
25 methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic
30 carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N=CH-]$
35 ester, vinyl ester, propargyl ester, p-nitrophenyl ester,

- 45 -

2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reaction derivatives can optionally be selected from them according to the kind of the compound (XII) to be used.

This reaction is usually carried out in the presence of a base.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g., magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, cesium carbonate, etc.), alkaline earth metal carbonate (e.g., magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g., sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g., sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g., magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate, (e.g., disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.) or the like, and an organic base such as trialkylamine (e.g., trimethylamine, triethylamine, etc.), pyridine, picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[5.4.0]undecene-5 or the like.

This reaction is usually carried out in a solvent such as benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform or any

- 46 -

other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

5

Process 7

The object compound (Ih) or a salt thereof can be prepared by reacting a compound (Ig) or its reactive derivative at the carboxy group or a salt thereof with a
10 compound (XIII) or its reactive derivative at the amino group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (Ig) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like.
15 Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.],
20 dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g., methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid
25 [e.g., benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(\text{CH}_3)_2\text{N}^+=\text{CH}-$] ester,
30 vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester,
35 carboxymethyl thioester, pyranyl ester, pyridyl ester,

- 47 -

piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (Ig) to be used.

Suitable salts of the compound (Ig) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

Suitable reactive derivative at the amino group of the compound (XIII) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (XIII) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (XIII) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (XIII) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (XIII) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (Ig) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide;

- 48 -

N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide;
N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;
5 N,N'-carbonylbis-(2-methylimidazole);
pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine; ethoxyacetylene;
1-alkoxy-1-chloroethylene; trialkylphosphite;
ethyl polyphosphate; isopropyl polyphosphate; phosphorous
10 oxychloride (phosphoryl chloride); phosphorus trichloride;
thionyl chloride; oxalyl chloride; lower alkyl haloformate
[e.g. ethyl chloroformate, isopropyl chloroformate, etc.];
triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt;
2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular
15 salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-
benzotriazole; so-called Vilsmeier reagent prepared by the
reaction of N,N-dimethylformamide with thionyl chloride,
phosgene, trichloromethyl chloroformate, phosphorus
oxychloride, methanesulfonyl chloride, etc.; or the like.

20 The reaction may also be carried out in the presence of
an inorganic or organic base such as an alkali metal
carbonate, alkali metal bicarbonate, tri(lower)alkylamine,
pyridine, N-(lower)alkylmorpholine,
N,N-di(lower)alkylbenzylamine, or the like.

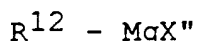
25 The reaction temperature is not critical, and the
reaction is usually carried out under cooling to warming.

Process 8

30 The compound (Ij) or a salt thereof can be prepared by
reacting the compound (Ii) or a salt thereof with Grignard
Reagent.

Suitable Grignard reagent to be used in the present
reaction may include the compound of the formula :

35



(XIV)

- 49 -

(wherein R¹² is lower alkyl, and
X" is halogen.)

This reaction is usually carried out in a solvent such
5 as tetrahydrofuran, toluene, methylene chloride, ethylene
dichloride, chloroform, dioxane, diethyl ether or any other
solvent which do not adversely affect the reaction, or the
mixture thereof.

The reaction temperature is not critical and the
10 reaction is usually carried out under cooling to heating.

Process 9

The object compound (I_l) or a salt thereof can be
prepared by subjecting a compound (I_k) or a salt thereof to
15 de-acylation reaction of acylamino group.

This reaction is carried out in accordance with a
conventional method such as hydrolysis, reduction or the
like.

The hydrolysis is preferably carried out in the presence
20 of a base or an acid including Lewis acid. Suitable base may
include an inorganic base and an organic base such as an
alkali metal [e.g., sodium, potassium, etc.], an alkaline
earth metal [e.g., magnesium, calcium, etc.], the hydroxide
or carbonate or bicarbonate thereof, trialkylamine [e.g.,
25 trimethylamine, triethylamine, etc.], picoline,
1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]-
octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g., formic
acid, acetic acid, propionic acid, trichloroacetic acid,
30 trifluoroacetic acid, etc.] and an inorganic acid [e.g.
hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen
chloride, hydrogen bromide, etc.].

The elimination using Lewis acid such as
trihaloacetic acid [e.g. trichloroacetic acid,
35 trifluoroacetic acid, etc.] or the like is preferably carried

- 50 -

out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g., tin, zinc, iron, etc.] or metallic compound [e.g., chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium, sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g., reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-

- 51 -

mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 10

The compound (Ik) or a salt thereof can be prepared by subjecting the compound (I_l) or its reactive derivative at the amino group, or a salt thereof to acylation reaction.

Suitable acylating agent to be used in the present acylation reaction may include the compound of the formula :



(wherein R^{13} is acyl)
or its reactive derivative, or a salt thereof.

Suitable reactive derivative at the amino group of the compound (I_l) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (I_l) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (I_l) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (I_l) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative of the compound (XV) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid

- 52 -

such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl, ester methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2^+N=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like.

These reactive derivatives can optionally be selected from them according to the kind of the compound (XV) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

When the compound (XV) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such

- 53 -

as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide); N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonyl-bis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorous oxychloride (phosphoryl chloride); phosphorous trichloride; thionyl chloride; oxalyl chloride; triphenylphosphite; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorous oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

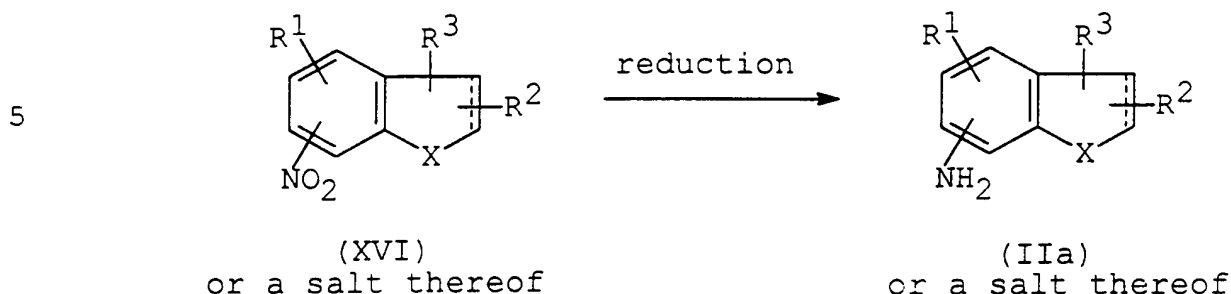
The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

25 Process 11

The compound (Im) or a salt thereof can be prepared by subjecting the compound (Ij) or a salt thereof to acylation reaction. This reaction can be carried out in a similar manner to that of the afore-mentioned Process 10, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 10.

In the starting compound (II), the compound (IIa) can be prepared according to the following reaction scheme.

- 54 -

Process A

10 wherein R^1 , R^2 , R^3 , ----- and X are each as defined above.

15 The reaction of this process can be carried out according to the method of Preparation 42 (1) mentioned below or the similar manners thereto.

20 Among the starting compounds (II) to (XVI), some of them are novel compounds. They can be prepared by the similar manners to those disclosed in Preparations mentioned later in the present specification, or any process known in this field of the art for preparing structurally analogous compounds thereto.

25 The compounds obtained by the above Processes 1 to 11 can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation or the like.

30 It is to be noted that each of the object compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and mixture thereof are included within the scope of this invention.

35 The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the object compound (I) or a pharmaceutically acceptable salt

- 55 -

thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient which is suitable for rectal; pulmonary (nasal or buccal inhalation); ocular; external (topical); oral administration; parenteral (including subcutaneous, intravenous and intramuscular) administrations; insufflation (including aerosols from metered dose inhalator); nebulizer; or dry powder inhalator.

The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers in a solid form such as granules, tablets, dragees, pellets, troches, capsules, or suppositories; creams; ointments; aerosols; powders for insufflation; in a liquid form such as solutions, emulsions, or suspensions for injection; ingestion; eye drops; and any other form suitable for use. And, if necessary, there may be included in the above preparation auxiliary substance such as stabilizing, thickening, wetting, emulsifying and coloring agents; perfumes or buffer; or any other commonly may be used as additives.

The object compound (I) or a pharmaceutically acceptable salt thereof include solvated compound [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compound (I) or a pharmaceutically acceptable salt thereof include both its crystal form and non-crystal form.

The object compound (I) or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

The pharmaceutical composition of the present invention can be manufactured by the conventional method in this field of the art. If necessary, the technique generally used in this field of the art for improving the bioavailability of a drug can be applied to the pharmaceutical composition of the present invention.

- 56 -

While the dosage of therapeutically effective amount of the object compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.001-100 mg of the object compound (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.001-100 mg of the object compound (I) per kg weight of a human being or an animal, in case of oral administration, a daily dose of 0.001-200 mg of the object compound (I) per kg weight of a human being or an animal is generally given for the prevention and/or the treatment of aforesaid diseases 1 to 4 times a day in a human being or an animal.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the representative compound of the compounds (I) is shown in the following.

Test Compound

(1) 7-(2,6-Dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan

Test (Bone organ culture) :

Test Method

Calvariae from Wistar rats were excised and cultured in wells of 12-well culture plates containing 2 ml of Dulbecco's modified minimum essential medium supplemented with 10% fetal bovine serum and 10^{-8} M human parathyroid hormone fragment (1-34) [PTH] in the presence of the test compound. In control dishes, PTH was not added. Control and PTH control were exposed to an equivalent concentration of the vehicle. Six days later, the concentration of calcium in the medium was measured by methylxlenol blue method and the percentage of inhibition of PTH-induced bone resorption was calculated

- 57 -

according to following formula.

$$\text{Inhibition (\%)} = \frac{[\text{Ca}] \text{ in PTH control dishes} - [\text{Ca}] \text{ in PTH control dishes} - [\text{Ca}] \text{ in the test compound dishes}}{[\text{Ca}] \text{ in control dishes}} \times 100$$

10 Test Result

Compound dose = 1×10^{-5} (M)

| Test Compound | Inhibition (%) |
|---------------|----------------|
| (1) | 100 |

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

- 58 -

Preparation 1 (1)

To a solution of pentan-3-one oxime (6.00 g) in dimethylformamide (30 ml) was added sodium hydride (60% oil suspension, 2.37 g) under ice cooling. After 15 minutes, to the above mixture was added dropwise 1-fluoro-2-nitrobenzene (5.98 g) in dimethylformamide (30 ml). The mixture was stirred for 3 hours at ambient temperature and poured into a mixture of ice and water. The separated oil was extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate and evaporated in vacuo to give pentan-3-one O-(2-nitrophenyl)oxime (10.51 g) as a brown oil.

NMR (CDCl₃, δ) : 1.12-1.30 (6H, m), 2.40 (2H, q, J=7Hz), 2.58 (2H, q, J=7Hz), 7.03 (1H, dt, J=1 and 8Hz), 7.53 (1H, dt, J=1 and 8Hz), 7.75 (1H, dd, J=1 and 8Hz), 7.95 (1H, dd, J=1 and 8Hz)

The following compounds [Preparations 1 (2) to (8)] were obtained according to a similar manner to that of Preparation 1 (1).

Preparation 1 (2)

Butan-2-one O-(4-carboxy-2-nitrophenyl)oxime
mp : 172-178°C

Preparation 1 (3)

Acetone O-(4-fluoro-2-nitrophenyl)oxime
mp : 76-77°C

NMR (CDCl₃, δ) : 2.05 (3H, s), 2.15 (3H, s), 7.27 (1H, m), 7.63-7.75 (2H, m)

Preparation 1 (4)

2,3,5,6-Tetrahydro-4H-thiopyran-4-one O-(2-nitrophenyl)oxime
mp : 71-73°C

- 59 -

NMR (CDCl₃, δ) : 2.68-2.75 (2H, m), 2.78-2.93 (4H, m), 3.07-3.17 (2H, m), 7.08 (1H, dt, J=1 and 8Hz), 7.54 (1H, dt, J=1 and 8Hz), 7.72 (1H, dd, J=1 and 8Hz), 7.95 (1H, dd, J=1 and 8Hz)

5

Preparation 1 (5)

Acetone O-(4-chloro-2-nitrophenyl)oxime

mp : 62-65°C

10 NMR (CDCl₃, δ) : 2.05 (3H, s), 2.15 (3H, s), 7.49 (1H, d, J=7Hz), 7.71 (1H, d, J=7Hz), 7.94 (1H, s)

Preparation 1 (6)

Ethyl 5-(2-nitrophenyl)oxyiminohexanoate

15

oil

Preparation 1 (7)

Cycloheptanone O-(2-nitrophenyl)oxime

20 NMR (CDCl₃, δ) : 1.55-1.68 (4H, m), 1.68-1.79 (4H, m), 2.52 (2H, t, J=6Hz), 2.82 (2H, t, J=6Hz), 7.02 (1H, t, J=8Hz), 7.52 (1H, t, J=8Hz), 7.73 (1H, d, J=8Hz), 7.91 (1H, d, J=8Hz)

Preparation 1 (8)

25

4-Ethoxycarbonylbutan-2-one O-(2-nitrophenyl)oxime

ESI Mass : 281 (M+H)⁺, 303 (M+Na)⁺Preparation 2 (1)

30 A mixture of 2-bromophenol (5 g), potassium carbonate (5.99 g) and 2-chlorocyclohexanone (4.22 g) in N,N-dimethylformamide was stirred at 60°C for 4 hours. The reaction mixture was poured into cold water and the separated oil was extracted with diethyl ether. The extract was washed with water, dried over sodium sulfate
35 and concentrated in vacuo. The residue was crystallized

- 60 -

from n-hexane to give 2-(2-bromophenoxy)cyclohexanone
(4.36 g).

mp : 72-73°C

5 NMR (CDCl₃, δ) : 1.74 (1H, m), 1.85-2.05 (2H,
m), 2.10-2.40 (4H, m), 2.70 (1H, m), 4.64 (1H,
dd, J=5 and 7.5Hz), 6.81 (1H, d, J=7.5Hz), 6.85
(1H, t, J=7.5Hz), 7.20 (1H, t, J=7.5Hz), 7.54
(1H, d, J=7.5Hz)

10 The following compounds [Preparations 2 (2) and (3)]
were obtained according to a similar manner to that of
Preparation 2 (1).

Preparation 2 (2)

15 3-(2-Acetylamino-4-nitrophenoxy)-2-butanone

NMR (CDCl₃, δ) : 1.70 (3H, d, J=6Hz), 2.22 (3H, s),
2.30 (3H, s), 4.87 (1H, q, J=6Hz), 6.78 (1H, d,
J=8Hz), 7.91 (1H, dd, J=2 and 8Hz), 8.19 (1H, br
s), 9.30 (1H, d, J=2Hz)

20

Preparation 2 (3)

2',6'-Dichloro-5-methyl-2-(1-methyl-2-oxopropyl)-
oxybenzophenone

mp : 111-113°C

25 NMR (CDCl₃, δ) : 0.97 (3H, d, J=7Hz), 1.95 (3H, s),
2.35 (3H, s), 4.42 (1H, q, J=7Hz), 6.53 (1H, d,
J=8Hz), 7.20-7.35 (4H, m), 7.93 (1H, s)

Preparation 3

30 2,6-Dichlorobenzoyl chloride (2.14 g) was added to a
solution of p-cresol (1.08 g) and triethylamine (1.11 g)
in dichloromethane (30 ml) dropwise at 4°C. The mixture
was stirred at ambient temperature overnight. The
reaction mixture was washed with aqueous saturated sodium
35 bicarbonate and brine, dried over sodium sulfate and

- 61 -

evaporated in vacuo to give 4-methylphenyl 2,6-dichlorobenzoate (2.73 g) as an oil.

NMR (CDCl_3 , δ) : 2.38 (3H, s), 7.17 (2H, d, $J=8\text{Hz}$),
7.25 (2H, d, $J=7\text{Hz}$), 7.30-7.45 (3H, m)

5

Preparation 4

A mixture of 4-methylphenyl 2,6-dichlorobenzoate (2.53 g) and aluminum chloride (2.4 g) in 1,2-dichloroethane (30 ml) was refluxed for 3 hours. The reaction mixture was cooled and poured into a mixture of ice and 1N hydrochloric acid. The separated oil was extracted with dichloromethane. The extract was washed with brine, aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 2',6'-dichloro-2-hydroxy-5-methylbenzophenone (1.72 g).

mp : 139-141°C
NMR (CDCl_3 , δ) : 2.22 (3H, s), 6.90 (1H, s),
7.00 (1H, d, $J=8\text{Hz}$), 7.30-7.45 (4H, m)

20

Preparation 5 (1)

To a suspension of butan-2-one O-(4-carboxy-2-nitrophenyl)oxime (4.5 g) in ethanol (45 ml) was added conc. sulfuric acid (6.8 ml) dropwise. The mixture was refluxed for 20 hours. The reaction mixture was cooled and poured into a mixture of ice and water. The separated oil was extracted with ethyl acetate. The extract was washed with brine, aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel. The first fractions were evaporated in vacuo and the residue was crystallized from hexane to give 5-ethoxycarbonyl-2-ethyl-7-nitrobenzo[b]furan (0.82 g).

30

35

- 62 -

mp : 82-83°C

NMR (CDCl₃, δ) : 1.42 (3H, t, J=8Hz), 1.46 (3H, t,
J=8Hz), 2.95 (2H, q, J=8Hz), 4.46 (2H, q,
J=8Hz), 6.61 (1H, s), 8.50 (1H, s), 8.75 (1H, s)

5

The second fractions were evaporated in vacuo and the
residue was crystallized from hexane to give 2,3-dimethyl-
5-ethoxycarbonyl-7-nitrobenzo[b]furan (1.2 g).

mp : 123-124°C

10 NMR (CDCl₃, δ) : 1.45 (3H, t, J=8Hz), 2.23 (3H,
s), 2.52 (3H, s), 4.47 (2H, q, J=8Hz), 8.40 (1H,
s), 8.73 (1H, s)

15 The following compounds [Preparations 5 (2) to (7)]
were obtained according to a similar manner to that of
Preparation 5 (1).

Preparation 5 (2)

5-Fluoro-2-methyl-7-nitrobenzo[b]furan

20 mp : 103-104°C

NMR (CDCl₃, δ) : 2.58 (3H, s), 6.52 (1H, s), 7.48
(1H, d, J=8Hz), 7.78 (1H, d, J=8Hz)

Preparation 5 (3)

25 7-Acetylamino-2,3-dimethyl-5-nitrobenzo[b]furan

mp : 197-198.5°C

NMR (CDCl₃, δ) : 2.20 (3H, s), 2.31 (3H, s), 2.45
(3H, s), 7.63 (1H, br s), 8.09 (1H, d, J=2Hz),
9.02 (1H, m)

30

Preparation 5 (4)

6-Nitro-3,4-dihydro-1H-thiopyrano[4,3-b]benzofuran

mp : 114-116°C

35 NMR (CDCl₃, δ) : 3.03-3.12 (2H, m), 3.12-3.23 (2H,
m), 3.77-3.80 (2H, m), 7.35 (1H, t, J=8Hz), 7.72

- 63 -

(1H, dd, J=1 and 8Hz), 8.10 (1H, dd, J=1 and 8Hz)

Preparation 5 (5)

5-Chloro-2-methyl-7-nitrobenzo[b]furan

mp : 153-154°C

5 NMR (CDCl₃, δ) : 2.58 (3H, s), 6.49 (1H, s), 7.73
(1H, s), 8.03 (1H, s)

Preparation 5 (6)

2-(3-Ethoxycarbonylpropyl)-7-nitrobenzo[b]furan

10 NMR (CDCl₃, δ) : 1.27 (3H, t, J=7Hz), 2.13 (2H,
quint., J=7Hz), 2.44 (2H, t, J=7Hz), 2.45 (2H,
t, J=7Hz), 4.14 (2H, q, J=7Hz), 6.57 (1H, s),
7.30 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 8.07
15 (1H, d, J=8Hz)

Preparation 5 (7)

1-Nitro-6,7,8,9-tetrahydro-5H-10-oxo-benzo[b]azulene

mp : 74-75°C

20 NMR (CDCl₃, δ) : 1.77-1.92 (6H, m), 2.68-2.74 (2H,
m), 3.00-3.08 (2H, m), 7.29 (1H, t, J=8Hz), 7.69
(1H, d, J=8Hz), 8.01 (1H, d, J=8Hz)

Preparation 6

25 A mixture of 2,4-bis(benzoylamino)phenol (6.0 g), 3-
chlorobutan-2-one (2.3 g) and potassium carbonate (5.0 g)
in N,N-dimethylformamide (30 ml) was stirred at 70°C for 3
hours. The reaction mixture was cooled and poured into
water. The separated oil was extracted with ethyl
acetate. The extract was washed with brine, dried over
30 sodium sulfate and evaporated in vacuo. To the residue
was added conc. sulfuric acid (30 ml) and the mixture was
stirred at 40°C for 7 hours. The reaction mixture was
cooled and poured into a mixture of ice and water. The
separated oil was extracted with ethyl acetate and the
35 extract was washed with brine, dried over sodium sulfate

- 64 -

and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 5,7-bis(benzoylamino)-2,3-dimethylbenzo[b]furan (3.7 g).

5 mp : 185-186°C

NMR (CDCl₃, δ) : 2.16 (3H, s), 2.40 (3H, s), 7.40-7.65 (6H, m), 7.85-8.00 (4H, m), 8.09 (2H, s), 8.15 (1H, s), 8.32 (1H, s)

10 Preparation 7

A mixture of pentan-3-one O-(2-nitrophenyl)oxime (10.50 g) in 10% hydrogen chloride-methanol (105 ml) was refluxed for 4 hours. After concentration in vacuo, the residue was extracted with ethyl acetate and water. The
15 obtained organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried over, sodium sulfate. After evaporation in vacuo, the residue was purified by column chromatography on silica gel (eluate; ethyl acetate:n-hexane = 1:6) to give a solid. The resulting
20 solid was triturated with a mixture of ethanol and water (2:1) and the precipitate was collected to give 2-ethyl-3-methyl-7-nitrobenzo[b]furan (4.44 g).

mp : 58-60°C

25 NMR (CDCl₃, δ) : 1.36 (3H, t, J=7Hz), 2.21 (3H, s), 2.87 (2H, q, J=7Hz) 7.29 (1H, t, J=8Hz), 7.70 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz)

Preparation 8

30 A solution of 4-ethoxycarbonylbutan-2-one O-(2-nitrophenyl)oxime (7.83 g) in 37% ethanolic hydrogen chloride (120 ml) was stirred at 80°C for 6 hours. The insoluble matter was filtered off and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was
35 crystallized from a mixture of ethanol (20 ml) and water

- 65 -

(4 ml) to give a mixture of 3-ethoxycarbonylmethyl-2-methyl-7-nitrobenzo[b]furan and 2-(2-ethoxycarbonylethyl)-7-nitrobenzo[b]furan (3.41 g).

To a solution of these mixture (2.0 g) in dichloromethane was added bromine (0.28 ml) in dichloromethane (1 ml) dropwise at 4°C. The mixture was stirred at 4°C for 30 minutes and at ambient temperature for 1 hour. The reaction mixture was washed with 5% aqueous sodium thiosulfate and aqueous saturated sodium bicarbonate, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel. The less polar fraction was combined and evaporated in vacuo to give 3-bromo-2-(2-ethoxycarbonylethyl)-7-nitrobenzo[b]furan (582 mg).

mp : 71-74°C

NMR (CDCl₃, δ) : 1.28 (3H, t, J=7Hz), 2.84 (2H, t, J=7Hz), 3.27 (2H, t, J=7Hz), 4.19 (2H, q, J=7Hz), 7.41 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 8.17 (1H, d, J=8Hz)

The more polar fraction was combined and evaporated in vacuo. The residue was crystallized from a mixture of ethanol and water to give 3-ethoxycarbonylmethyl-2-methyl-7-nitrobenzo[b]furan (832 mg).

mp : 64-68°C

NMR (CDCl₃, δ) : 1.25 (3H, t, J=7Hz), 2.56 (3H, s), 3.63 (2H, s), 4.17 (2H, q, J=7Hz), 7.32 (1H, t, J=8Hz), 7.80 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz)

Preparation 9

A mixture of 2-methyl-7-nitrobenzo[b]furan (2.66 g), N-bromosuccinimide (3.21 g) and 2,2'-azobis-(2,4-dimethyl-4-methoxyvaleronitrile) (270 mg) in dichloromethane (30 ml) was refluxed for 1 hour. The reaction mixture was washed with aqueous saturated sodium bicarbonate and

- 66 -

brine, dried over sodium sulfate and concentrated in vacuo. The residue was crystallized from diethyl ether to give 2-bromomethyl-7-nitrobenzo[b]furan (3.3 g).

mp : 146-147°C

5 NMR (CDCl₃, δ) : 4.66 (2H, s), 6.92 (1H, s), 7.38 (1H, t, J=8Hz), 7.87 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz)

Preparation 10

10 A mixture of 2-bromomethyl-7-nitrobenzo[b]furan (512 mg), ethyl mercaptoacetate (0.24 ml) and potassium carbonate (552 mg) in N,N-dimethylformamide (4 ml) was stirred at ambient temperature for 2 hours. To the reaction mixture was added cold water and the separated solid was collected, washed with water and dried to give 2-ethoxycarbonylmethylthiomethyl-7-nitrobenzo[b]furan (546 mg).

mp : 84-87°C

20 NMR (CDCl₃, δ) : 1.30 (3H, t, J=8Hz), 3.31 (2H, s), 4.08 (2H, s), 4.20 (2H, q, J=8Hz), 6.79 (1H, s), 7.34 (1H, t, J=8Hz), 7.82 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz)

Preparation 11 (1)

25 A solution of 2-(3-ethoxycarbonylpropyl)-7-nitrobenzo[b]furan (1.0 g) in a mixture of aqueous 1N-sodium hydroxide (7.2 ml) and ethanol (5 ml) was stirred at 50°C for 1 hour. The reaction mixture was diluted with water and acidified with 4N-hydrochloric acid. The separated solid was collected, washed with water and dried to give 2-(3-carboxypropyl)-7-nitrobenzo[b]furan (752 mg).

mp : 180-182°C

35 NMR (CDCl₃, δ) : 2.11-2.21 (2H, m), 2.52 (2H, t, J=7Hz), 2.98 (2H, t, J=7Hz), 6.59 (1H, s), 7.30 (1H, t, J=8Hz), 7.80 (1H, d, J=8Hz), 8.07 (1H,

- 67 -

d, J=8Hz)

The following compound was obtained according to a similar manner to that of Preparation 11 (1).

5

Preparation 11 (2)

2-Carboxymethylthiomethyl-7-nitrobenzo[b]furan

mp : 92-93°C

10 NMR (DMSO-d₆, δ) : 3.37 (2H, s), 4.11 (2H, s), 7.02 (1H, s), 7.47 (1H, t, J=8Hz), 8.06 (1H, d, J=8Hz), 8.11 (1H, d, J=8Hz)

Preparation 12 (1)

15 A solution of 2-(3-carboxypropyl)-7-nitrobenzo[b]furan (500 mg) in thionyl chloride (5 ml) was refluxed for 1.5 hours. The reaction mixture was diluted with toluene and concentrated in vacuo. The residue was dissolved in dichloromethane (15 ml) and to the mixture was added aluminum chloride (435 mg) at 4°C. The mixture
20 was stirred at ambient temperature for 2 hours and partitioned between 1N-hydrochloric acid and dichloromethane. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography
25 on silica gel and the obtained oil was crystallized from a mixture of ethyl acetate and n-hexane to give 6-nitro-1-oxo-1,2,3,4-tetrahydrodibenzofuran (282 mg).

mp : 122-123.5°C

30 NMR (CDCl₃, δ) : 2.30-2.41 (2H, m), 2.68 (2H, t, J=7Hz), 3.20 (2H, t, J=7Hz), 7.49 (1H, t, J=8Hz), 8.18 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)

The following compound was obtained according to a similar manner to that of Preparation 12 (1).

35

- 68 -

Preparation 12 (2)

1,2-Dihydro-6-nitro-1-oxo-4H-thiopyrano[3,4-b]benzo-
[b]furan

mp : 210-211°C

5 NMR (CDCl₃, δ) : 3.56 (2H, s), 4.13 (2H, s), 7.52
(1H, t, J=8Hz), 8.20 (1H, d, J=8Hz), 8.45 (1H,
d, J=8Hz)

Preparation 13

10 A mixture 1-hydroxyimino-6-nitro-1,2,3,4-
tetrahydrodibenzofuran (425 mg) p-toluenesulfonyl chloride
(394 mg) and triethylamine (521 mg) in dichloromethane was
stirred at ambient temperature for 2 hours. The mixture
was directly purified by column chromatography on silica
15 gel and the obtained oil was crystallized from diisopropyl
ether to give 6-nitro-1,2,3,4-tetrahydro-1-p-
toluenesulfonyloxyiminodibenzofuran (609 mg).

mp : 175-182°C (dec.)

20 NMR (CDCl₃, δ) : 2.09-2.19 (2H, m), 2.46 (3H, s),
2.65 (4/5H, m), 2.90 (6/5H, t, J=6Hz), 2.98-3.11
(2H, m), 7.32-7.42 (3H, m), 7.89-8.00 (2H, m),
8.07-8.19 (8/5H, m), 8.61 (2/5H, d, J=8Hz)

Preparation 14

25 A mixture of 2-(2-boromophenoxy)cyclohexanone (4.306
g) and polyphosphoric acid (40 g) was stirred at 50°C for
4 hours. The reaction mixture was poured into cold water
and the separated oil was extracted with ethyl acetate.
The extract was washed with water, aqueous saturated
30 sodium bicarbonate and brine, dried over sodium sulfate
and concentrated in vacuo. The residue was purified by
column chromatography on silica gel. The appropriate
fractions were combined and concentrated in vacuo to give
6-bromo-1,2,3,4-tetrahydrodibenzofuran (3.49 g) as an oil.

35 NMR (CDCl₃, δ) : 1.85 (2H, m), 1.95 (2H, m), 2.61

- 69 -

(2H, m), 2.80 (2H, m), 7.06 (1H, t, J=7.5Hz),
7.33 (1H, d, J=7.5Hz), 7.35 (1H, d, J=7.5Hz)

Preparation 15

5 To a suspension of magnesium (345 mg) in
tetrahydrofuran (5 ml) was added 6-bromo-1,2,3,4-
tetrahydrodibenzofuran (3.39 g) in tetrahydrofuran (15 ml)
dropwise. The mixture was refluxed for 1 hour and cooled
to 4°C. Dry ice (2.7 g) was added to the mixture and the
10 mixture was stirred at ambient temperature for 30 minutes.
To the mixture was added 3.6% hydrochloric acid and
chloroform. The organic layer was separated, dried over
sodium sulfate and concentrated in vacuo. The residue was
crystallized from n-hexane to give 1,2,3,4-
15 tetrahydrodibenzofuran-6-carboxylic acid (2.60 g).

mp : 197-198°C

NMR (CDCl₃, δ) : 1.88 (2H, m), 1.97 (2H, m), 2.64
(2H, m), 2.85 (2H, m), 7.28 (1H, t, J=7.5Hz),
7.65 (1H, d, J=7.5Hz), 7.95 (1H, d, J=7.5Hz)

20

Preparation 16

A mixture of 7-carboxy-2,3-dimethylbenzo[b]furan (2
g) and N,N-dimethylformamide (1 drop) in thionyl chloride
(10 ml) was refluxed for 2 hours. The reaction mixture
25 was cooled and concentrated in vacuo. The crystalline
residue was triturated with n-hexane to give
7-chlorocarbonyl-2,3-dimethylbenzo[b]furan (2.17 g).

mp : 75-77°C

NMR (CDCl₃, δ) : 2.19 (3H, s), 2.47 (3H, s), 7.32
30 (1H, t, J=7.5Hz), 7.72 (1H, d, J=7.5Hz), 8.03
(1H, d, J=7.5Hz)

Preparation 17

Sodium borohydride (38 mg) was added to a solution of
35 6-nitro-1-oxo-1,2,3,4-tetrahydrodibenzofuran (231 mg) in a

- 70 -

mixture of ethanol (1.5 ml) and N,N-dimethylformamide (1.5 ml). The mixture was stirred at ambient temperature for 20 minutes, diluted with water and acidified with 3.6% hydrochloric acid. The separated oil was extracted with ethyl acetate and the extract was washed with aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated in vacuo. The residue was crystallized from diisopropyl ether to give 1-hydroxy-6-nitro-1,2,3,4-tetrahydrodibenzofuran (175 mg).

mp : 127-129°C

NMR (CDCl₃, δ) : 1.90-2.05 (2H, m), 2.05-2.20 (2H, m), 2.88 (2H, m), 5.08 (1H, m), 7.35 (1H, t, J=7.5Hz), 7.97 (1H, d, J=7.5Hz), 8.08 (1H, d, J=7.5Hz)

Preparation 18 (1)

To a mixture of 2-methyl-7-nitrobenzo[b]furan (177 mg) and aluminum chloride (200 mg) in dichloromethane (5 ml) was added dropwise propionyl chloride (0.18 ml). The mixture was stirred at ambient temperature for 3 hours and poured into a mixture of ice and 1N-hydrochloric acid. The separated oil was extracted with dichloromethane and the extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from diethyl ether to give 2-methyl-7-nitro-3-propionylbenzo[b]furan (215 mg).

mp : 128-129°C

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7Hz), 2.92 (3H, s), 2.99 (2H, q, J=7Hz), 7.35 (1H, t, J=7Hz), 8.13 (1H, d, J=7Hz), 8.42 (1H, d, J=7Hz)

The following compounds [Preparations 18 (2) to (8)] were obtained according to a similar manner to that of Preparation 18 (1).

- 71 -

Preparation 18 (2)

3-Acetyl-5-fluoro-2-methyl-7-nitrobenzo[b]furan

mp : 144-146°C

NMR (CDCl₃, δ) : 2.64 (3H, s), 2.93 (3H, s), 7.88
(1H, d, J=8Hz), 8.20 (1H, d, J=8Hz)Preparation 18 (3)

3-Acetyl-5-chloro-2-methyl-7-nitrobenzo[b]furan

mp : 171-172°C

NMR (CDCl₃, δ) : 2.65 (3H, s), 2.92 (3H, s),
8.12 (1H, s), 8.46 (1H, s)Preparation 18 (4)

3-Ethoxalyl-2-methyl-7-nitrobenzo[b]furan

mp : 88-89°C

NMR (CDCl₃, δ) : 1.45 (3H, t, J=8Hz), 2.82 (3H, s),
4.49 (2H, q, J=8Hz), 7.48 (1H, t, J=8Hz), 8.19
(1H, d, J=8Hz), 8.39 (1H, d, J=8Hz)Preparation 18 (5)

3-Benzoyl-2-methyl-7-nitrobenzo[b]furan

mp : 92-93°C

NMR (CDCl₃, δ) : 2.60 (3H, s), 7.38 (1H, t, J=8Hz),
7.53 (2H, t, J=8Hz), 7.65 (1H, t, J=8Hz), 7.80
(2H, d, J=8Hz), 7.89 (1H, d, J=8Hz), 8.13 (1H,
d, J=8Hz)Preparation 18 (6)

3-Butyryl-2-methyl-7-nitrobenzo[b]furan

mp : 121.5-123°C

NMR (CDCl₃, δ) : 1.03 (3H, t, J=7Hz), 1.80 (2H, sex,
J=7Hz), 2.84-2.91 (5H, m), 7.42 (1H, t, J=8Hz),
8.11 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz)Preparation 18 (7)

- 72 -

3-Cyclohexylcarbonyl-2-methyl-7-nitrobenzo[b]furan

mp : 164-166°C

NMR (CDCl₃, δ) : 1.25-2.00 (10H, m), 2.89 (3H, s),
3.01 (1H, m), 7.45 (1H, t, J=8Hz), 8.13 (1H, d,
J=8Hz), 8.32 (1H, d, J=8Hz)

Preparation 18 (8)

3-Chloroacetyl-2-methyl-7-nitrobenzo[b]furan

mp : 167-168°C

NMR (CDCl₃, δ) : 2.96 (3H, s), 4.60 (2H, s), 7.50
(1H, t, J=7Hz), 8.18 (1H, d, J=7Hz), 8.38 (1H,
d, J=7Hz)

Preparation 19

To a mixture of 2-methyl-7-nitrobenzo[b]furan (1.77 g) and aluminum chloride (2.66 g) in dichloromethane (40 ml) was added dropwise a solution of dichloromethyl methyl ether (3.6 ml) in dichloromethane (10 ml). The mixture was stirred at ambient temperature for 30 minutes and the reaction mixture was poured into a mixture of ice and 1N-hydrochloric acid. The separated oil was extracted with dichloromethane and the extract was washed with brine, aqueous saturated sodium bicarbonate and brine. Then, the solution was dried over sodium sulfate and evaporated in vacuo. The obtained oil was crystallized from diethyl ether to give 3-formyl-2-methyl-7-nitrobenzo[b]furan (1.83 g).

mp : 166-167°C

NMR (CDCl₃, δ) : 2.91 (3H, s), 7.50 (1H, t, J=7Hz),
8.18 (1H, d, J=7Hz), 8.50 (1H, d, J=7Hz), 10.28
(1H, s)

Preparation 20

Into a mixture of 2-methyl-7-nitrobenzo[b]furan (200 mg) and aluminum chloride (301 mg) in dichloromethane was

- 73 -

passed hexafluoroacetone gas which was made from hexafluoroacetone trihydrate (4.7 ml) and conc. sulfuric acid (15 ml). The mixture was stirred at ambient temperature for 4 hours and then, cooled to 4°C. To the mixture was added 1N-hydrochloric acid dropwise. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from n-hexane to give 3-(1-hydroxy-2,2,2-trifluoro-1-trifluoromethylethyl)-2-methyl-7-nitrobenzo[b]furan (265 mg).

mp : 79.5-80.5°C

NMR (CDCl₃, δ) : 2.76 (3H, s), 3.79 (1H, s), 7.37 (1H, t, J=7.5Hz), 8.10 (1H, m), 8.13 (1H, d, J=7.5Hz)

FAB-Mass : (m/z) = 344 (M⁺+1)

Preparation 21

A mixture of 3-chloroacetyl-2-methyl-7-nitrobenzo[b]furan (431 mg) and thiourea (194 mg) in ethanol (10 ml) was refluxed for 1.5 hours. The separated solid was collected, washed with ethanol and dried to give 3-(2-aminothiazol-4-yl)-2-methyl-7-nitrobenzo[b]furan hydrochloride (485 mg).

mp : 222-223°C

NMR (DMSO-d₆, δ) : 2.72 (3H, s), 7.07 (1H, s), 7.54 (1H, t, J=7Hz), 8.18 (1H, d, J=7Hz), 8.23 (1H, d, J=7Hz)

Preparation 22

A mixture of 3-(2-aminothiazol-4-yl)-2-methyl-7-nitrobenzo[b]furan hydrochloride (468 mg), acetic anhydride (306 mg) and triethylamine (455 mg) in 1,2-dichloroethane (20 ml) was refluxed for 1 day. To the reaction mixture was added methanol and the mixture was

- 74 -

evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 3-(2-acetylaminothiazol-4-yl)-2-methyl-7-nitrobenzo[b]furan (305 mg).

mp : 260-261°C

NMR (DMSO-d₆, δ) : 2.20 (3H, s), 2.81 (3H, s), 7.53 (1H, s), 7.53 (1H, t, J=7Hz), 8.17 (1H, d, J=7Hz), 8.46 (1H, d, J=7Hz)

Preparation 23 (1)

A mixture of 3-formyl-2-methyl-7-nitrobenzo[b]furan (1.83 g) and sodium borohydride (200 mg) in methanol (40 ml) was stirred at ambient temperature for 2 hours. The reaction mixture was poured into cold water. The separated oil was extracted with dichloromethane. The extract was washed with brine, dried and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 3-hydroxymethyl-2-methyl-7-nitrobenzo[b]furan (1.38 g) as a solid.

mp : 129-131°C

NMR (CDCl₃, δ) : 1.62 (1H, t, J=6Hz), 2.59 (3H, s), 4.83 (2H, d, J=6Hz), 7.34 (1H, t, J=7Hz), 7.95 (1H, d, J=7Hz), 8.08 (1H, d, J=7Hz)

The following compound was obtained according to a similar manner to that of Preparation 23 (1).

Preparation 23 (2)

3-(1-Ethoxycarbonyl)hydroxymethyl-2-methyl-7-nitrobenzo[b]furan

mp : 73-78°C

NMR (CDCl₃, δ) : 1.20 (3H, t, J=8Hz), 2.62 (3H, s), 3.46 (1H, d, J=4Hz), 4.22 (2H, m), 5.35 (1H, d, J=4Hz), 7.31 (1H, t, J=8Hz), 7.85 (1H, d,

- 75 -

J=8Hz), 8.07 (1H, d, J=8Hz)

Preparation 24

5 A mixture of 3-chloromethyl-2-methyl-7-nitrobenzo[b]furan (200 mg) and sodium thiomethoxide (68 mg) in N,N-dimethylformamide (2 ml) was stirred at ambient temperature for 2 hours. The reaction mixture was poured into cold water and the separated oil was extracted with ethyl acetate. The extract was washed with brine, dried
10 over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 2-methyl-3-methylthiomethyl-7-nitrobenzo[b]furan (144 mg).

15 NMR (CDCl₃, δ) : 2.03 (3H, s), 2.57 (3H, s), 3.78 (2H, s), 7.34 (1H, t, J=7.5Hz), 7.92 (1H, d, J=7.5Hz), 8.08 (1H, d, J=7.5Hz)

Preparation 25

20 Sodium hydride (60%, 54 mg) was added to a solution of 3-acetylamino-2-methyl-7-nitrobenzo[b]furan (280 mg) in N,N-dimethylformamide (3 ml) at 4°C. The mixture was stirred for 30 minutes and to the mixture was added iodoethane (240 mg). The mixture was stirred at ambient temperature for 2 hours. The reaction mixture was poured
25 into cold water and the separated oil was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 3-(N-acetyl-N-ethylamino)-2-methyl-7-nitrobenzo[b]furan as a crystalline solid (310 mg).

mp : 114-116°C

30 NMR (CDCl₃, δ) : 1.14 (3H, t, J=7.5Hz), 1.88 (3H, s), 2.54 (3H, s), 3.65 (1H, qd, J=7.5 and 13.5Hz), 3.87 (1H, qd, J=7.5 and 13.5Hz), 7.41
35 (1H, t, J=8Hz), 7.69 (1H, d, J=8Hz), 8.15 (1H,

- 76 -

d, J=8Hz)

Preparation 26

5 A solution of 3-(N-acetyl-N-ethylamino)-2-methyl-7-nitrobenzo[b]furan (310 mg) and borane-methyl sulfide complex (0.13 ml, 1.42 mmol) in tetrahydrofuran (6 ml) was stirred at 4°C for 30 minutes, at ambient temperature for 1 hour and at 50°C for 15 minutes. Then, the mixture was cooled to 4°C and to the mixture was added 1N-hydrochloric acid. The mixture was stirred at ambient temperature for 1 hour and neutralized with aqueous saturated sodium bicarbonate. The separated oil was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 3-diethylamino-2-methyl-7-nitrobenzo[b]furan as an oil (249 mg).

20 NMR (CDCl₃, δ) : 0.99 (6H, t, J=7.5Hz), 2.50 (3H, s), 3.23 (4H, q, J=7.5Hz), 7.25 (1H, t, J=7.5Hz), 7.84 (1H, d, J=7.5Hz), 8.02 (1H, d, J=7.5Hz)

Preparation 27 (1)

25 To a solution of 3-acetyl-7-amino-2-methylbenzo[b]furan (2.4 g) in dichloromethane (30 ml) was added acetic anhydride (1.6 g) dropwise. The solution was stirred at ambient temperature for 1 hour and evaporated in vacuo. Toluene was added to the residue and the solution was evaporated in vacuo. The residue was crystallized from diethyl ether to give 3-acetyl-7-acetylamino-2-methylbenzo[b]furan (2.92 g).

mp : 180-181°C

35 NMR (CDCl₃, δ) : 2.29 (3H, s), 2.63 (3H, s), 2.79 (3H, s), 7.29 (1H, t, J=7Hz), 7.55-7.65 (2H, m), 8.13 (1H, d, J=7Hz)

- 77 -

The following compound was obtained according to a similar manner to that of Preparation 27 (1).

Preparation 27(2)

5 6-Acetyl-1-nitro-6,7,8,9-tetrahydro-5H-10-oxo-6-aza-benzo[b]azulene

mp : 106-109°C

10 NMR (CDCl₃, δ) : 2.07-2.20 (5H, m), 3.12-3.24 (2H, m), 3.79-3.92 (2H, m), 4.62 (2/3H, s), 4.81 (4/3H, s), 7.38 (1H, m), 7.75 (1/3H, d, J=8Hz), 7.88 (2/3H, d, J=8Hz), 8.11 (1H, m)

Preparation 28 (1)

15 A mixture of 7-carboxy-2,3-dimethylbenzo[b]furan (400 mg) and borane-dimethyl sulfide complex (0.4 ml) in tetrahydrofuran (6 ml) was stirred at ambient temperature for 40 hours. The mixture was quenched with 1N-hydrochloric acid and extracted with dichloromethane. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from n-hexane to give 2,3-dimethyl-7-hydroxymethylbenzo[b]furan (322 mg).

mp : 64-65°C

25 NMR (CDCl₃, δ) : 1.93 (1H, t, J=7Hz), 2.15 (3H, s), 2.40 (3H, s), 4.98 (2H, d, J=8Hz), 7.14-7.21 (2H, m), 7.36 (1H, dd, J=1.5 and 8Hz)

30 The following compound was obtained according to a similar manner to that of Preparation 28 (1).

Preparation 28 (2)

35 1-Nitro-6,7,8,9-tetrahydro-5H-10-oxo-6-aza-benzo[b]azulene

mp : 79-81°C

- 78 -

NMR (CDCl₃, δ) : 1.90-2.00 (2H, m), 3.11-3.24 (4H, m), 4.02 (2H, s), 7.30 (1H, t, J=8Hz), 7.68 (1H, d, J=8Hz), 8.05 (1H, d, J=8Hz)

5 Preparation 29

To a solution of 3-acetyl-7-acetylamino-2-methylbenzo[b]furan (2.92 g) in tetrahydrofuran (60 ml) was added a 3M solution of methylmagnesium bromide in diethyl ether (12.7 ml) dropwise with ice cooling. The solution was stirred at ambient temperature for 5 hours and to the solution was added aqueous saturated ammonium chloride. Then, the mixture was poured into water and the separated oil was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from methanol to give 7-acetylamino-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan (1.82 g).

mp : 141-143°C

20 NMR (CDCl₃, δ) : 1.20 (6H, s), 1.33 (1H, s), 2.28 (3H, s), 2.60 (3H, s), 7.14 (1H, t, J=7Hz), 7.39 (1H, d, J=7Hz), 7.58 (1H, br), 8.05 (1H, d, J=7Hz)

25 Preparation 30

A solution of 3-formyl-2-methyl-7-nitrobenzo[b]furan (200 mg) and (carboethoxymethylene)triphenylphosphorane (434 mg) in dioxane (3 ml) was stirred at ambient temperature for 1 hour. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel. The obtained oil was crystallized from diisopropyl ether to give 3-(2-ethoxycarbonylethenyl)-2-methyl-7-nitrobenzo[b]furan (226 mg).

35 mp : 148-150°C

- 79 -

5 NMR (CDCl₃, δ) : 1.37 (3H, t, J=7.5Hz), 2.70 (3H, s), 4.30 (2H, q, J=7.5Hz), 6.50 (1H, d, J=14Hz), 7.43 (1H, t, J=8Hz), 7.78 (1H, d, J=14Hz), 8.09 (1H, d, J=8Hz), 8.14 (1H, d, J=8Hz)

Preparation 31

10 10%-Palladium on carbon (30 mg) was added to a solution of 3-(2-ethoxycarbonylethenyl)-2-methyl-7-nitrobenzo[b]furan (210 mg) in a mixture of dioxane (3 ml) and ethanol (1 ml). The mixture was hydrogenated at 3 atoms for 3 hours and the catalyst was filtered off. The filtrate was concentrated in vacuo to give 7-amino-3-(2-ethoxycarbonylethyl)-2-methylbenzo[b]furan (195 mg).

15 NMR (CDCl₃, δ) : 1.23 (3H, t, J=7.5Hz), 2.40 (3H, s), 2.62 (2H, t, J=7.5Hz), 2.91 (2H, t, J=7.5Hz), 3.89 (2H, br s), 4.12 (2H, q, J=7.5Hz), 6.58 (1H, d, J=8Hz), 6.87 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz)

20

Preparation 32

25 A solution of 3-(2-ethoxycarbonyl-3-oxobutyl)-2-methyl-7-nitrobenzo[b]furan (170 mg) in a mixture of ethanol (5 ml) and aqueous 1N-sodium hydroxide (5 ml) was refluxed for 1 hour. The reaction mixture was cooled and the separated solid was collected, washed with water and dried to give 2-methyl-7-nitro-3-(3-oxobutyl)benzo[b]furan (105 mg).

mp : 99-100°C

30 NMR (CDCl₃, δ) : 2.12 (3H, s), 2.52 (3H, s), 2.77 (2H, t, J=6Hz), 2.92 (2H, t, J=6Hz), 7.31 (1H, t, J=7Hz), 7.74 (1H, d, J=7Hz), 8.05 (1H, d, J=7Hz)

35 Preparation 33

- 80 -

3-Hydroxymethyl-2-methyl-7-nitrobenzo[b]furan (1.0 g) was added to thionyl chloride (1.8 ml) with ice cooling. The mixture was stirred at ambient temperature for 30 minutes and concentrated in vacuo. To the residue was added toluene and the mixture was concentrated again. The residue was crystallized from a mixture of diethyl ether and n-hexane to give 3-chloromethyl-2-methyl-7-nitrobenzo[b]furan (1.01 g).

mp : 132-133°C

NMR (CDCl₃, δ) : 2.61 (3H, s), 4.73 (2H, s), 7.40 (1H, t, J=7Hz), 7.91 (1H, d, J=7Hz), 8.12 (1H, d, J=7Hz)

Preparation 34

A mixture of 3-chloromethyl-2-methyl-7-nitrobenzo[b]furan (410 mg) and potassium phthalimide (506 mg) in N,N-dimethylformamide (10 ml) was stirred at ambient temperature for 3 hours. Then, the mixture was poured into cold water and the separated solid was collected, washed with water and dried to give 2-methyl-7-nitro-3-phthalimidomethylbenzo[b]furan (585 mg).

mp : 231-233°C

NMR (CDCl₃, δ) : 2.80 (3H, s), 4.92 (2H, s), 7.33 (1H, t, J=7Hz), 7.65-7.78 (2H, m), 7.78-7.90 (2H, m), 8.04 (1H, d, J=7Hz), 8.18 (1H, d, J=7Hz)

Preparation 35

A mixture of 3-chloromethyl-2-methyl-7-nitrobenzo[b]furan (226 mg) and triethyl phosphite (0.52 ml) was stirred at 100°C for 6 hours. The reaction mixture was cooled and concentrated in vacuo and to the residue was added toluene. The mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel. The obtained oil was

- 81 -

crystallized from diisopropyl ether to give 3-(diethoxyphosphorylmethyl)-2-methyl-7-nitrobenzo[b]furan (93 mg).

mp : 102-103°C

5 NMR (CDCl₃, δ) : 1.25 (6H, t, J=7Hz), 2.57 (3H, d, J=4Hz), 3.15 (2H, d, J=20Hz), 4.05 (4H, quint., J=7Hz), 7.33 (1H, t, J=7Hz), 7.88 (1H, d, J=7Hz), 8.08 (1H, d, J=7Hz)

10 Preparation 36

To a solution of sodium (52 mg) in ethanol (5 ml) was added ethyl acetoacetate (293 mg) and 3-chloromethyl-2-methyl-7-nitrobenzo[b]furan (339 mg). The mixture was stirred at 60°C for 3 hours, cooled and poured into cold
15 water. The pH of the aqueous solution was adjusted to 3 with 1N-hydrochloric acid and the separated oil was extracted with dichloromethane. The extract was washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography
20 on silica gel and the obtained oil was crystallized from n-hexane to give 3-(2-ethoxycarbonyl-3-oxobutyl)-2-methyl-7-nitrobenzo[b]furan (205 mg).

mp : 97-99°C

25 NMR (CDCl₃, δ) : 1.21 (3H, t, J=7Hz), 2.22 (3H, s), 2.52 (3H, s), 3.21 (3H, m), 3.79 (1H, t, J=7Hz), 4.16 (2H, q, J=7Hz), 7.32 (1H, t, J=7Hz), 7.77 (1H, d, J=7Hz), 8.07 (1H, d, J=7Hz)

Preparation 37

30 A mixture of 2-methyl-7-nitro-3-phthalimidomethylbenzo[b]furan (575 mg) and hydrazine monohydrate (172 mg) in ethanol (10 ml) was refluxed for 5 hours. The reaction mixture was cooled, acidified with 1N-hydrochloric acid and filtered. The filtrate was
35 neutralized with aqueous saturated sodium bicarbonate and

- 82 -

the ethanol in the mixture was evaporated in vacuo. The separated solid was collected, washed with water and dried to give 3-aminomethyl-2-methyl-7-nitrobenzo[b]furan (290 mg).

5 mp : 134-138°C

NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.58 (3H, s), 3.95 (2H, s), 7.38 (1H, t, J=7Hz), 7.91 (1H, d, J=7Hz), 8.09 (1H, d, J=7Hz)

10 Preparation 38 (1)

A solution of 5,7-diamino-2,3-dimethylbenzo[b]furan (970 mg), di-tert-butyl dicarbonate (2.0 g) and triethylamine (668 mg) in dichloromethane was stirred at ambient temperature for 8 hours. The reaction mixture was
15 evaporated in vacuo and the residue was purified by column chromatography on silica gel. The obtained oil was crystallized from a mixture of diethyl ether and n-hexane to give 7-amino-5-(tert-butoxycarbonylamino)-2,3-dimethylbenzo[b]furan (1.10 g).

20 mp : 177-178°C

NMR (CDCl₃, δ) : 1.51 (9H, s), 2.09 (3H, s), 2.32 (3H, s), 3.85 (2H, br s), 6.39 (1H, s), 6.60 (1H, s), 6.84 (1H, s)

25 Preparation 38 (2)

A mixture of 3-aminomethyl-2-methyl-7-nitrobenzo[b]furan (278 mg) and di-tert-butyl dicarbonate (353 mg) in dichloromethane (5 ml) was stirred at ambient temperature for overnight. The reaction mixture was
30 concentrated in vacuo and the residue was purified by column chromatography on silica gel. The obtained oil was crystallized from a mixture of diisopropyl ether and n-hexane to give 3-tert-butoxycarbonylamino-2-methyl-7-nitrobenzo[b]furan (313 mg).

35 mp : 120-122°C

- 83 -

NMR (CDCl₃, δ) : 1.46 (9H, s), 2.58 (3H, s), 4.41 (2H, d, J=6Hz), 4.72 (1H, br s), 7.33 (1H, t, J=7Hz), 7.90 (1H, d, J=7Hz), 8.08 (1H, d, J=7Hz)

5 Preparation 39 (1)

A mixture of 3-acetyl-2-methyl-7-nitrobenzo[b]furan (413 mg), hydroxylamine hydrochloride (393 mg) and sodium bicarbonate (792 mg) in ethanol (10 ml) was refluxed for 30 minutes. The reaction mixture was cooled and water was added to the solution. The separated solid was collected, washed with water and dried to give 3-(1-hydroxyiminoethyl)-2-methyl-7-nitrobenzo[b]furan (320 mg).
mp : 158-162°C

15 The following compound was obtained according to a similar manner to that of Preparation 39 (1).

Preparation 39 (2)

1-Hydroxyimino-6-nitro-1,2,3,4-tetrahydrodibenzofuran
20 mp : 174°C (dec.)
NMR (CDCl₃, δ) : 2.07-2.20 (2H, m), 2.86 (2H, t, J=6Hz), 3.01 (2H, t, J=6Hz), 7.38 (1H, t, J=8Hz), 8.11 (1H, d, J=8Hz), 8.29 (1H, d, J=8Hz)

25 Preparation 40 (1)

A solution of 3-(1-hydroxyiminoethyl)-2-methyl-7-nitrobenzo[b]furan (200 mg) in trifluoroacetic acid (3 ml) was refluxed for 1.5 hours. The reaction mixture was concentrated in vacuo and the residue was crystallized from a mixture of methanol and water to give 3-acetylamino-2-methyl-7-nitrobenzo[b]furan (185 mg).
mp : >250°C
NMR (CDCl₃:CD₃OD = 1:1, δ) : 2.23 (3H, s), 2.50 (3H, s), 7.33 (1H, t, J=7Hz), 7.75 (1H, d, J=7Hz),
35 8.70 (1H, d, J=7Hz)

- 84 -

Preparation 40 (2)

A solution of 6-nitro-1,2,3,4-tetrahydro-1-p-toluenesulfonyloxyiminodibenzofuran (1.1 g) in trifluoroacetic acid (22 ml) was refluxed for 3 hours.

5 The mixture was evaporated in vacuo and poured into a mixture of ice and water. The separated oil was extracted with chloroform. The extract was washed with aqueous saturated sodium bicarbonate, dried over sodium sulfate and evaporated in vacuo. The residue was purified by
10 column chromatography on silica gel and the obtained crude solid was triturated with a hot mixture of ethyl acetate and n-hexane (1:1) to give 1-nitro-6,7,8,9-tetrahydro-5H-10-oxo-6-aza-benzo[b]azulen-5-one (550 mg).

mp : 230-233°C

15 NMR (CDCl₃, δ) : 2.21-2.31 (2H, m), 3.33 (2H, t, J=6Hz), 3.50 (2H, q, J=5Hz), 6.33 (1H, m), 7.42 (1H, t, J=8Hz), 8.13 (1H, d, J=8Hz), 8.63 (1H, d, J=8Hz)

20 Preparation 41

A mixture of 6-nitro-1-oxo-1,2,3,4-tetrahydrodibenzofuran (300 mg) and sodium azide (102 mg) in trifluoroacetic acid (3 ml) was stirred at 60°C for 5 hours. The reaction mixture was concentrated in vacuo and
25 the residue was purified by column chromatography on silica gel. The obtained oil was crystallized from diisopropyl ether to give 1-nitro-6,7,8,9-tetrahydro-5H-10-oxo-5-aza-benzo[b]azulen-6-one (70 mg).

mp : >250°C

30 NMR (CDCl₃, δ) : 2.14 (2H, m), 2.68-2.78 (2H, m), 3.20 (2H, t, J=6Hz), 7.40 (1H, t, J=8Hz), 7.99 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz)

Preparation 42 (1)

35 To a solution of 3-bromo-2-methyl-7-

- 85 -

nitrobenzo[b]furan (300 mg) and acetic acid (776 mg) in a mixture of ethanol (6 ml) and dioxane (1.5 ml) was added iron (722 mg) at 50°C. The mixture was refluxed for 1.5 hours and the insoluble material was filtered off. The filtrate was evaporated in vacuo with toluene. The residue was extracted with a mixture of ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was separated and it was extracted with ethyl acetate from aqueous layer. The organic layer was combined and washed with saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate, and evaporated in vacuo to give 7-amino-3-bromo-2-methylbenzo[b]furan (262 mg) as a white solid.

mp : 70-71°C

NMR (CDCl₃, δ) : 2.48 (3H, s), 3.82 (2H, br s), 6.63 (1H, dd, J=1 and 8Hz), 6.86 (1H, dd, J=1 and 8Hz), 7.09 (1H, t, J=8Hz)

The following compounds [Preparations 42 (2) to (14)] were obtained according to a similar manner to that of Preparation 42 (1).

Preparation 42 (2)

3-Acetyl-7-amino-2-methylbenzo[b]furan

mp : 112-113°C

NMR (CDCl₃, δ) : 2.63 (3H, s), 2.78 (3H, s), 3.95 (2H, br s), 6.66 (1H, d, J=7Hz), 7.12 (1H, t, J=7Hz), 7.29 (1H, d, J=7Hz)

Preparation 42 (3)

7-Amino-3-hydroxymethyl-2-methylbenzo[b]furan

mp : 117-121°C

NMR (CDCl₃, δ) : 1.51 (1H, t, J=5Hz), 2.45 (3H, s), 3.90 (2H, br s), 4.72 (2H, d, J=5Hz), 6.60 (1H, d, J=7Hz), 6.95-7.10 (2H, m)

- 86 -

Preparation 42 (4)

3-Acetyl-7-amino-5-fluoro-2-methylbenzo[b]furan

mp : 133-134°C

5 NMR (CDCl₃, δ) : 2.59 (3H, s), 2.76 (3H, s), 4.05
(2H, br s), 6.39 (1H, d, J=8Hz), 6.97 (1H, d,
J=8Hz)

Preparation 42 (5)

6-Amino-3,4-dihydro-1H-thiopyrano[4,3-b]benzo[b]furan

10 NMR (CDCl₃, δ) : 3.02 (4H, s), 3.75 (2H, s), 3.90
(2H, br s), 6.62 (1H, dd, J=1 and 8Hz), 6.83
(1H, dd, J=1 and 8Hz), 7.02 (1H, t, J=8Hz)

Preparation 42 (6)

15 6-Amino-1,2-dihydro-1-oxo-4H-thiopyrano[3,4-b]benzo-
[b]furan

mp : 161-163°C

20 NMR (CDCl₃, δ) : 3.49 (2H, s), 3.92 (2H, br s), 3.99
(2H, s), 6.70 (1H, d, J=8Hz), 7.15 (1H, t,
J=8Hz), 7.48 (1H, d, J=8Hz)

Preparation 42 (7)

7-Amino-2-methyl-3-methylthiomethylbenzo[b]furan

25 NMR (CDCl₃, δ) : 2.00 (3H, s), 2.43 (3H, s), 3.71
(2H, s), 3.80-3.97 (2H, m), 6.60 (1H, d, J=7Hz),
6.97-7.04 (2H, m)

Preparation 42 (8)

3-Acetyl-7-amino-5-chloro-2-methylbenzo[b]furan

30 mp : 162-163°C

NMR (CDCl₃, δ) : 2.60 (3H, s), 2.76 (3H, s), 4.02
(2H, br s), 6.65 (1H, s), 7.28 (1H, s)

Preparation 42 (9)

35 7-Amino-3-butyryl-2-methylbenzo[b]furan

- 87 -

mp : 109-111°C

NMR (CDCl₃, δ) : 1.04 (3H, t, J=7Hz), 1.80 (2H, sex,
J=7Hz), 2.77 (3H, s), 2.91 (2H, t, J=7Hz), 3.46
(2H, br s), 6.77 (1H, d, J=8Hz), 7.12 (1H, t,
J=8Hz), 7.27 (1H, m)

Preparation 42 (10)

7-Amino-3-(1-ethoxycarbonyl)hydroxymethyl-2-
methylbenzo[b]furan

mp : 103-105°C

NMR (CDCl₃, δ) : 1.19 (3H, t, J=8Hz), 2.49 (3H, s),
3.37 (1H, br s), 3.88 (2H, br s), 4.21 (2H, m),
5.28 (1H, s), 6.58 (1H, d, J=8Hz), 6.90 (1H, d,
J=8Hz), 6.98 (1H, t, J=8Hz)

Preparation 42 (11)

7-Amino-3-(2-ethoxycarbonylethenyl)-2-
methylbenzo[b]furan

mp : 103-105°C

NMR (CDCl₃, δ) : 1.35 (3H, t, J=7.5Hz), 2.57 (3H,
s), 3.94 (2H, br s), 4.29 (2H, q, J=7.5Hz), 6.48
(1H, d, J=14Hz), 6.66 (1H, d, J=8Hz), 7.10 (1H,
t, J=8Hz), 7.19 (1H, d, J=8Hz), 7.77 (1H, d,
J=14Hz)

Preparation 42 (12)

6-Amino-1-oxo-1,2,3,4-tetrahydrodibenzofuran

mp : 118-119.5°C

NMR (CDCl₃, δ) : 2.28 (2H, quint., J=7Hz), 2.60 (2H,
t, J=7Hz), 3.03 (2H, t, J=7Hz), 3.95 (2H, m),
6.68 (1H, d, J=8Hz), 7.12 (1H, t, J=8Hz), 7.45
(1H, d, J=7Hz)

Preparation 42 (13)

7-Amino-3-ethoxycarbonylmethyl-2-methylbenzo[b]furan

- 88 -

NMR (CDCl₃, δ) : 1.23 (3H, t, J=7Hz), 2.42 (3H, s),
3.57 (2H, s), 3.88 (2H, br s), 4.14 (2H, q,
J=7Hz), 6.58 (1H, d, J=8Hz), 6.90 (1H, d,
J=8Hz), 7.00 (1H, t, J=8Hz)

5

Preparation 42 (14)

7-Amino-3-bromo-2-(2-ethoxycarbonyl-ethyl)-
benzo[b]furan

10 NMR (CDCl₃, δ) : 1.26 (3H, t, J=7Hz), 2.76 (2H, t,
J=7Hz), 3.17 (2H, t, J=7Hz), 3.91 (2H, br s),
4.17 (2H, q, J=7Hz), 6.64 (1H, d, J=8Hz), 6.88
(1H, d, J=8Hz), 7.09 (1H, t, J=8Hz)

Preparation 43 (1)

15 To a solution of 2-ethyl-3-methyl-7-
nitrobenzo[b]furan (1.00 g) in a mixture of methanol (15
ml) and dioxane (10 ml) was added 10% palladium carbon
(100 mg) and the above mixture was hydrogenated at 3 atm
for 1 hour. The catalyst was filtered off and the
20 filtrate was evaporated in vacuo to give 7-amino-2-ethyl-
3-methylbenzo[b]furan (858 mg) as an oil.

25 NMR (CDCl₃, δ) : 1.30 (3H, t, J=8Hz), 2.14 (3H,
s), 2.74 (2H, q, J=8Hz), 3.88 (2H, br s), 6.59
(1H, d, J=6Hz), 6.86 (1H, d, J=6Hz), 7.01 (1H,
t, J=6Hz)

The following compounds [Preparations 43 (2) to (17)]
were obtained according to a similar manner to that of
Preparation 43 (1).

30

Preparation 43 (2)

7-Amino-2-methyl-3-propionylbenzo[b]furan

mp : 126-127°C

35 NMR (CDCl₃, δ) : 1.25 (3H, t, J=7Hz), 2.78 (3H,
s), 2.98 (2H, q, J=7Hz), 3.97 (2H, br s), 6.66

- 89 -

(1H, t, J=7Hz), 7.12 (1H, d, J=7Hz), 7.28 (1H, d, J=7Hz)

Preparation 43 (3)

5 7-Amino-2,3-dimethyl-5-ethoxycarbonylbenzo[b]furan

mp : 137-140°C

NMR (CDCl₃, δ) : 1.42 (3H, t, J=8Hz), 2.15 (3H, s), 2.39 (3H, s), 3.95 (2H, br s), 4.38 (2H, q, J=8Hz), 7.30 (1H, s), 7.60 (1H, s)

10

Preparation 43 (4)

7-Amino-3-(diethoxyphosphorylmethyl)-2-methylbenzo[b]furan

mp : 105-109°C

15 NMR (CDCl₃, δ) : 1.22 (6H, t, J=7Hz), 2.46 (3H, d, J=4Hz), 3.10 (2H, d, J=20Hz), 3.89 (2H, br s), 4.01 (4H, quint., J=7Hz), 6.59 (1H, d, J=7Hz), 6.93 (1H, d, J=7Hz), 7.01 (1H, t, J=7Hz)

20 Preparation 43 (5)

3-Acetylamino-7-amino-2-methylbenzo[b]furan

mp : 183-184°C

25 NMR (CDCl₃: CD₃OD = 9:1, δ) : 2.20 (3H, s), 2.37 (3H, s), 6.60 (1H, d, J=7Hz), 6.80 (1H, d, J=7Hz), 7.00 (1H, t, J=7Hz)

Preparation 43 (6)

7-Amino-3-tert-butoxycarbonylaminomethyl-2-methylbenzo[b]furan

30 mp : 110-111°C

NMR (CDCl₃, δ) : 1.46 (9H, s), 2.45 (3H, s), 3.90 (2H, br s), 4.33 (2H, d, J=6Hz), 4.65 (1H, br), 6.60 (1H, d, J=7Hz), 6.92 (1H, d, J=7Hz), 7.03 (1H, t, J=7Hz)

35

- 90 -

Preparation 43 (7)

7-Amino-2-methyl-3-(3-oxobutyl)benzo[b]furan

mp : 75-76°C

5 NMR (CDCl₃, δ) : 2.12 (3H, s), 2.40 (3H, s), 2.77
(2H, m), 2.85 (2H, m), 3.89 (2H, br s), 6.58
(1H, d, J=7Hz), 6.83 (1H, d, J=7Hz), 7.00 (1H,
t, J=7Hz)

Preparation 43 (8)

10 7-Amino-3-diethylamino-2-methylbenzo[b]furan

NMR (CDCl₃, δ) : 0.96 (6H, t, J=7.5Hz), 2.38 (3H,
s), 3.10 (4H, q, J=7.5Hz), 3.89 (2H, br s), 6.55
(1H, d, J=7.5Hz), 6.29 (1H, d, J=7.5Hz), 6.98
(1H, t, J=7.5Hz)

15

Preparation 43 (9)7-Amino-3-(1-hydroxy-2,2,2-trifluoro-1-
trifluoromethylethyl)-2-methylbenzo[b]furan

mp : 167.5-168.5°

20 NMR (CDCl₃, δ) : 2.00 (3H, br s), 2.63 (3H, s), 6.53
(1H, d, J=7.5Hz), 7.02 (1H, t, J=7.5Hz), 7.16
(1H, d, J=7.5Hz)

FAB-Mass : (m/z) = 314 (M⁺+1)

25 Preparation 43 (10)

7-Amino-3-benzoyl-2-methylbenzo[b]furan

mp : 150-151°C

30 NMR (CDCl₃, δ) : 2.57 (3H, s), 3.97 (2H, br s), 6.63
(1H, d, J=8Hz), 6.73 (1H, d, J=8Hz), 6.99 (1H,
t, J=8Hz), 7.48 (2H, t, J=8Hz), 7.59 (1H, t,
J=8Hz), 7.80 (2H, d, J=8Hz)

Preparation 43 (11)

7-Amino-3-cyclohexylcarbonyl-2-methylbenzo[b]furan

35 mp : 125-126°C

- 91 -

NMR (CDCl₃, δ) : 1.20-1.55 (5H, m), 1.60-2.05 (5H, m), 2.87 (3H, s), 3.06 (1H, m), 3.97 (2H, br s), 6.65 (1H, d, J=8Hz), 7.11 (1H, t, J=8Hz), 7.18 (1H, d, J=8Hz)

5

Preparation 43 (12)

6-Amino-1,2,3,4-tetrahydrodibenzofuran

NMR (CDCl₃, δ) : 1.77-2.00 (4H, m), 2.54-2.79 (4H, m), 3.86 (2H, m), 6.58 (1H, d, J=8Hz), 6.84 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz)

10

Preparation 43 (13)

1-Amino-6,7,8,9-tetrahydro-5H-10-oxo-benzo[b]azulene

mp : 89-94°C

NMR (CDCl₃, δ) : 1.73-1.89 (6H, m), 2.65 (2H, t, J=5Hz), 2.91 (2H, t, J=5Hz), 3.86 (2H, br s), 6.55 (1H, d, J=8Hz), 6.83 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz)

15

20 Preparation 43 (14)

1-Amino-6,7,8,9-tetrahydro-5H-10-oxo-5-aza-benzo[b]azulen-6-one

mp : 220-223°C

NMR (CDCl₃, δ) : 2.11-2.20 (2H, m), 2.71 (2H, t, J=6Hz), 3.06 (2H, t, J=6Hz), 3.82 (2H, br s), 6.63 (1H, d, J=8Hz), 6.83 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.43 (1H, br s)

25

Preparation 43 (15)

6-Amino-1-hydroxy-1,2,3,4-tetrahydrodibenzofuran

mp : 127-128°C

NMR (CDCl₃, δ) : 1.8-2.2 (4H, m), 2.6-2.9 (2H, m), 3.90 (2H, br s), 5.02 (1H, m), 6.62 (1H, t, J=4Hz), 7.05 (2H, d, J=4Hz)

35

- 92 -

Preparation 43 (16)

3-(2-Acetylaminothiazol-4-yl)-7-amino-2-methylbenzo[b]furan

mp : 203-204°C

5 NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.22 (3H, s), 2.65 (3H, s), 6.68 (1H, d, J=7Hz), 7.01 (1H, s), 7.07 (1H, t, J=7Hz), 7.19 (1H, d, J=7Hz) .

Preparation 43 (17)

10 6-Acetyl-1-amino-6,7,8,9-tetrahydro-5H-10-oxo-6-aza-benzo[b]azulene

mp : 137-140°C

15 NMR (CDCl₃, δ) : 1.98-2.17 (5H, m), 2.97-3.08 (2H, m), 3.70-4.00 (4H, m), 4.51 (4/3H, s), 4.75 (2/3H, s), 6.60 (1H, t, J=8Hz), 6.81-7.08 (2H, m)

Preparation 44

20 To a suspension of 5,7-bis(benzoylamino)-dimethylbenzo[b]furan (2.5 g) in ethanol (18 ml) was added conc. hydrochloric acid (9 ml) and the mixture was refluxed for 36 hours. The reaction mixture was cooled and evaporated in vacuo. The residue was dissolved in water and the solution was washed with ethyl acetate. The aqueous layer was neutralized with aqueous saturated sodium bicarbonate and the separated oil was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo to give 5,7-diamino-2,3-dimethylbenzo[b]furan.

30 mp : 151-152°C

NMR (CDCl₃, δ) : 2.03 (3H, s), 2.31 (3H, s),
6.00 (1H, s), 6.15 (1H, s)

Preparation 45 (1)

35 A suspension of 7-acetyl-amino-3-(1-hydroxy-1-

- 93 -

methylethyl)-2-methylbenzo[b]furan (1.82 g) in a mixture of ethanol (15 ml) and 3N-aqueous sodium hydroxide (10 ml) was refluxed for 20 hours. The reaction mixture was cooled, diluted with water (20 ml) and evaporated in vacuo until the ethanol of the solution was removed. The separated solid was collected, washed with water and dried to give 7-amino-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan (1.42 g).

mp : 127-128°C

NMR (CDCl₃, δ) : 1.70 (6H, s), 1.84 (1H, s), 2.59 (3H, s), 3.90 (2H, br s), 6.58 (1H, d, J=7Hz), 6.99 (1H, t, J=7Hz), 7.09 (1H, d, J=7Hz)

The following compound was obtained according to a similar manner to that of Preparation 45 (1).

Preparation 45 (2)

7-Amino-2,3-dimethyl-5-nitrobenzo[b]furan

mp : 156-157°C

NMR (CDCl₃, δ) : 2.17 (3H, s), 2.41 (3H, s), 4.12 (2H, br s), 7.48 (1H, d, J=2Hz), 7.29 (1H, d, J=2Hz)

to be continued on the next page

- 94 -

Example 1 (1)

A mixture of 7-amino-2-ethyl-3-methylbenzo[b]furan (858 mg), 2,6-dichlorobenzoyl chloride (1.23 g) and triethylamine (1.23 g) in 1,2-dichloroethane (17 ml) was stirred for 3 hours at 70°C. The mixture was diluted with dichloromethane, washed with diluted hydrochloric acid and brine, dried over sodium sulfate, and evaporated in vacuo to give a solid. The residue solid was crystallized from a mixture of ethanol (20 ml) and water (2 ml) to give 7-(2,6-dichlorobenzoylamino)-2-ethyl-3-methylbenzo[b]furan (610 mg).

mp : 169-170°C

NMR (CDCl₃, δ) : 1.27 (3H, t, J=7Hz), 2.18 (3H, s), 2.74 (2H, q, J=7Hz), 7.23 (2H, m), 7.29-7.44 (3H, m), 7.81 (1H, br s), 8.28 (1H, m)

The following compounds [Examples 1 (2) to (76)] were obtained according to a similar manner to that of Example 1 (1).

Example 1 (2)

7-(2,6-Dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 169-171°C

NMR (CDCl₃, δ) : 2.46 (3H, s), 6.40 (1H, m), 7.18-7.29 (2H, m), 7.32-7.44 (3H, m), 7.82 (1H, br s), 8.29 (1H, dd, J=1 and 8Hz)

Example 1 (3)

7-(2,6-Dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan

mp : 195-196°C

NMR (CDCl₃, δ) : 2.16 (3H, s), 2.38 (3H, s), 7.23 (2H, m), 7.33-7.44 (3H, m), 7.81 (1H, br s), 8.28 (1H, m)

Example 4 (4)

- 95 -

3-Bromo-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 218-219°C

5 NMR (CDCl₃, δ) : 2.49 (3H, s), 7.21-7.30 (2H, m),
7.30-7.45 (3H, m), 7.80 (1H, br s), 8.35 (1H, dd, J=1 and 8Hz)

Example 1 (5)

10 7-(2,6-Dichlorobenzoylamino)-2,3-dimethylbenzo[b]thiophene

mp : 235-236°C

NMR (CDCl₃, δ) : 2.32 (3H, s), 2.50 (3H, s),
7.30-7.53 (6H, m), 7.90 (1H, dd, J=1 and 8Hz)

15 Example 1 (6)

7-(2,6-Dichlorobenzoylamino)-2,3-dimethyl-5-ethoxycarbonylbenzo[b]furan

mp : 192-193°C

20 NMR (CDCl₃, δ) : 1.43 (3H, t, J=8Hz), 2.20 (3H, s), 2.40 (3H, s), 4.44 (2H, q, J=8Hz), 7.25-7.45 (3H, m), 7.82 (1H, br s), 8.02 (1H, s), 8.94 (1H, s)

Example 1 (7)

25 5-(tert-Butoxycarbonylamino)-7-(2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan

mp : 192-194°C

30 NMR (CDCl₃, δ) : 1.53 (9H, s), 2.12 (3H, s), 2.35 (3H, s), 6.60 (1H, s), 7.30-7.45 (3H, s), 7.68 (1H, s), 7.80 (1H, s), 7.98 (1H, s)

Example 1 (8)

35 3-Acetyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 216-217°C

- 96 -

NMR (CDCl₃, δ) : 2.67 (3H, s), 2.79 (3H, s),
7.30-7.50 (4H, m), 7.72 (1H, d, J=7Hz), 7.83
(1H, br s), 8.35 (1H, d, J=7Hz)

5 Example 1 (9)

7-(2,6-Dichlorobenzoylamino)-3-hydroxymethyl-2-
methylbenzo[b]furan

mp : 183-184°C

10 NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.46 (3H, s), 4.72
(2H, s), 7.25 (1H, t, J=7Hz), 7.30-7.50 (4H, m),
8.16 (1H, d, J=7Hz)

Example 1 (10)

15 7-(2,6-Dichlorobenzoylamino)-2-methyl-3-
propionylbenzo[b]furan

mp : 216-217°C

20 NMR (CDCl₃, δ) : 1.28 (3H, t, J=7Hz), 2.79 (3H,
s), 2.99 (2H, q, J=7Hz), 7.30-7.45 (4H, m), 7.70
(1H, d, J=7Hz), 7.83 (1H, br s), 8.36 (1H, d,
J=7Hz)

Example 1 (11)

25 7-(2,6-Dichloro-3-methoxybenzoylamino)-3-(1-hydroxy-
i-methylethyl)-2-methylbenzo[b]furan

mp : 167-168°C

30 NMR (CDCl₃, δ) : 1.71 (6H, s), 1.80 (1H, s), 2.58
(3H, s), 3.94 (3H, s), 6.96 (1H, d, J=8Hz), 7.22
(1H, t, J=8Hz), 7.35 (1H, d, J=8Hz), 7.46 (1H,
d, J=8Hz), 7.79 (1H, br s), 8.29 (1H, d, J=8Hz)

Example 1 (12)

3-Acetyl-7-(2,6-dichlorobenzoylamino)-5-fluoro-2-
methylbenzo[b]furan

mp : 223-229°C

35 NMR (CDCl₃, δ) : 2.62 (3H, s), 2.77 (3H, s),

- 97 -

7.30-7.45 (4H, m), 7.84 (1H, br s), 8.22 (1H, d, J=9Hz)

Example 1 (13)

5 3-Acetyl-7-(2-chloro-6-methylbenzoylamino)-2-methylbenzo[b]furan

mp : 181-182°C

10 NMR (CDCl₃, δ) : 2.48 (3H, s), 2.66 (3H, s), 2.78 (3H, s), 7.21 (1H, m), 7.32 (2H, d, J=6Hz), 7.38 (1H, t, J=8Hz), 7.70 (1H, d, J=8Hz), 7.80 (1H, br s), 8.35 (1H, d, J=8Hz)

Example 1 (14)

15 7-(2,6-Dichlorobenzoylamino)-3-(diethoxyphosphorylmethyl)-2-methylbenzo[b]furan

mp : 172-174°C

20 NMR (CDCl₃, δ) : 1.25 (6H, t, J=7Hz), 2.45 (3H, d, J=4Hz), 3.12 (2H, d, J=20Hz), 4.03 (4H, quint., J=7Hz), 7.20-7.45 (5H, m), 7.82 (1H, br s), 8.30 (1H, d, J=7Hz)

Example 1 (15)

25 6-(2,6-Dichloro-3-nitrobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran

mp : 244-245°C

30 NMR (CDCl₃, δ) : 1.81-2.00 (4H, m), 2.60-2.69 (2H, m), 2.69-2.77 (2H, m), 7.24-7.29 (2H, m), 7.56 (1H, dd, J=4 and 8Hz), 7.86-7.93 (2H, m), 8.23 (1H, m)

Example 1 (16)

35 6-(2,6-Dichlorobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran

mp : 195-196°C

NMR (CDCl₃, δ) : 1.78-2.01 (4H, m), 2.59-2.77

- 98 -

(4H, m), 7.20-7.30 (2H, m), 7.32-7.43 (3H, m),
7.85 (1H, br s), 8.30 (1H, m)

Example 1 (17)

5 6-(2,6-Dichlorobenzoylamino)-3,4-dihydro-1H-
thiopyrano[4,3-b]benzofuran

mp : 215-216°C

NMR (CDCl₃, δ) : 3.00-3.06 (4H, m), 3.78 (2H, br
s), 7.20-7.31 (3H, m), 7.32-7.46 (2H, m), 7.82
10 (1H, br s), 8.43 (1H, dd, J=1 and 6Hz)

Example 1 (18)

6-(3,5-Dichloroisonicotinoylamino)-1,2,3,4-
tetrahydrodibenzofuran

15 mp : 201-203°C

NMR (CDCl₃, δ) : 1.82-2.00 (4H, m), 2.60-2.68
(2H, m), 2.68-2.77 (2H, m), 7.25 (2H, m), 7.88
(1H, br s), 8.22 (1H, dd, J=1 and 7Hz), 8.60
(2H, s)

20

Example 1 (19)

6-(2,6-Dichlorobenzoylamino)-1,2-dihydro-1-oxo-4H-
thiopyrano[3,4-b]benzo[b]furan

mp : >250°C

25 NMR (CDCl₃, δ) : 3.52 (2H, s), 4.00 (2H, s),
7.30-7.45 (4H, m), 7.77 (1H, br s), 7.90 (1H, d,
J=8Hz), 8.33 (1H, d, J=8Hz)

Example 1 (20)

30 6-(2-Chloro-6-methylbenzoylamino)-1-hydroxy-1,2,3,4-
tetrahydrodibenzofuran

mp : 179-180°C

NMR (CDCl₃, δ) : 1.71 (1H, d, J=7.5Hz), 1.85-2.20
(4H, m), 2.46 (3H, s), 2.72 (2H, m), 5.05 (1H,
35 m), 7.18 (1H, d, J=7.5Hz), 7.2-7.35 (3H, m),

- 99 -

7.42 (1H, d, J=7.5Hz), 7.80 (1H, br s), 8.30
(1H, d, J=7.5Hz)

Example 1 (21)

5 6-(2-Bromo-6-methylbenzoylamino)-1-hydroxy-1,2,3,4-
tetrahydrodibenzofuran

mp : 186-187°C

NMR (CDCl₃, δ) : 1.71 (1H, d, J=7.5Hz), 1.8-2.2
 (4H, m), 2.47 (3H, s), 2.73 (2H, m), 5.05 (1H,
10 br s), 7.15-7.25 (2H, m), 7.30 (1H, d, J=7.5Hz),
 7.43 (1H, d, J=7.5Hz), 7.45 (1H, t, J=7.5Hz),
 7.77 (1H, br s), 8.30 (1H, d, J=7.5Hz)

Example 1 (22)

15 1-(2,6-Dichlorobenzoylamino)-6,7,8,9-tetrahydro-5H-
10-oxobenzo[b]azulene

mp : 191-192°C

NMR (CDCl₃, δ) : 1.72-1.90 (6H, m), 2.63-2.73
 (2H, m), 2.87-2.95 (2H, m), 7.19-7.28 (2H, m),
20 7.30-7.42 (3H, m), 7.80 (1H, br s), 8.27 (1H, d,
 J=8Hz)

Example 1 (23)

25 1-(2,6-Dichlorobenzoylamino)-6,7,8,9-tetrahydro-5H-
10-oxo-5-azabenzo[b]azulen-6-one

mp : >250°C

NMR (CDCl₃, δ) : 2.12-2.21 (2H, m), 2.70 (2H, t,
 J=6Hz), 3.07 (2H, t, J=6Hz), 7.30 (1H, t,
 J=8Hz), 7.34-7.45 (4H, m), 8.19 (1H, d, J=8Hz)

Example 1 (24)

6-(2,6-Dichlorobenzoylamino)-1-oxo-1,2,3,4-
tetrahydrodibenzofuran

mp : >250°C

35 NMR (CDCl₃, δ) : 2.29 (2H, quint., J=7Hz), 2.29

- 100 -

(2H, t, J=7Hz), 3.04 (2H, t, J=7Hz), 7.34-7.44
(4H, m), 7.80 (1H, br s), 7.87 (1H, d, J=8Hz),
8.32 (1H, d, J=8Hz)

5 Example 1 (25)

7-(2,6-Dichlorobenzoylamino)-2,3-dimethyl-5-
nitrobenzo[b]furan

mp : >250°C

10 NMR (CDCl₃, δ) : 2.21 (3H, s), 2.43 (3H, s),
7.35-7.47 (3H, m), 7.89 (1H, br s), 8.19 (1H, d,
J=2Hz), 9.24 (1H, d, J=2Hz)

Example 1 (26)

15 3-Acetylamino-7-(2,6-dichlorobenzoylamino)-2-
methylbenzo[b]furan

mp : >250°C

20 NMR (DMSO-d₆, δ) : 2.09 (3H, s), 2.33 (3H, s),
7.15-7.30 (2H, m), 7.40-7.65 (3H, m), 7.78 (1H,
d, J=7Hz), 9.58 (1H, s)

Example 1 (27)

3-tert-Butoxycarbonylaminomethyl-7-(2,6-
dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 188-189°C

25 NMR (CDCl₃, δ) : 1.46 (9H, s), 2.45 (3H, s), 4.38
(2H, d, J=6Hz), 4.70 (1H, br s), 7.20-7.45 (5H,
m), 7.82 (1H, br s), 8.31 (1H, d, J=7Hz)

Example 1 (28)

30 7-(2,6-Dichlorobenzoylamino)-3-diethylamino-2-
methylbenzo[b]furan

mp : 134-135°C

35 NMR (CDCl₃, δ) : 0.97 (6H, t, J=7.5Hz), 2.38 (3H,
s), 3.12 (4H, q, J=7.5Hz), 7.19 (1H, t,
J=7.5Hz), 7.13-7.43 (4H, m), 7.84 (1H, br s),

- 101 -

8.28 (1H, d, J=7.5Hz)

Example 1 (29)

7-(2,6-Dichlorobenzoylamino)-2-methyl-3-(3-oxobutyl)benzo[b]furan

mp : 209-210°C

NMR (CDCl₃, δ) : 2.12 (3H, s), 2.41 (3H, s), 2.80 (2H, t, J=6Hz), 2.88 (2H, t, J=6Hz), 7.20-7.30 (2H, m), 7.30-7.40 (3H, m), 7.81 (1H, br s), 8.30 (1H, d, J=7Hz)

Example 1 (30)

3-Acetyl-5-chloro-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 241-242°C

NMR (CDCl₃, δ) : 2.63 (3H, s), 2.78 (3H, s), 7.30-7.45 (3H, m), 7.73 (1H, s), 7.80 (1H, br s), 8.43 (1H, s)

Example 1 (31)

7-(2,6-Dichlorobenzoylamino)-3-(2-ethoxycarbonylethyl)-2-methylbenzo[b]furan

mp : 132-134°C

NMR (CDCl₃, δ) : 1.23 (3H, t, J=6.5Hz), 2.42 (3H, s), 2.64 (2H, t, J=6.5Hz), 2.95 (2H, t, J=6.5Hz), 4.13 (2H, q, J=6.5Hz), 7.25 (2H, d, J=6Hz), 7.31-7.43 (3H, m), 7.82 (1H, br s), 8.29 (1H, dd, J=4.5 and 6Hz)

Example 1 (32)

7-(2,6-Dichlorobenzoylamino)-2-methyl-3-methylthiomethylbenzo[b]furan

mp : 207-208.5°C

NMR (CDCl₃, δ) : 2.04 (3H, s), 2.44 (3H, s), 3.75 (2H, s), 7.24-7.28 (1H, m), 7.33-7.44 (4H, m),

- 102 -

7.80 (1H, br s), 8.30 (1H, d, J=7.5Hz)

Example 1 (33)

7-(2,6-Dichlorobenzoylamino)-3-(2-
5 ethoxycarbonylethenyl)-2-methylbenzo[b]furan

mp : 207-208°C

NMR (CDCl₃, δ) : 1.36 (3H, t, J=7.5Hz), 2.59 (3H,
s), 4.28 (2H, q, J=7.5Hz), 6.52 (1H, d, J=15Hz),
7.31-7.43 (4H, m), 7.58 (1H, d, J=8Hz), 7.75
10 (1H, d, J=15Hz), 7.83 (1H, br s), 8.37 (1H, d,
J=8Hz)

Example 1 (34)

7-(2,6-Dichlorobenzoylamino)-3-(1-hydroxy-2,2,2-
15 trifluoro-1-trifluoromethylethyl)-2-methylbenzo[b]furan

mp : 208-209°C

NMR (CDCl₃, δ) : 2.65 (3H, s), 3.57 (1H, s),
7.25-7.45 (4H, m), 7.50 (1H, m), 7.80 (1H, br
s), 8.33 (1H, d, J=7.5Hz)

20 FABB-Mass : (e/z) = 486 (M⁺+1)

Example 1 (35)

3-Butyryl-7-(2,6-dichlorobenzoylamino)-2-
methylbenzo[b]furan

25 mp : 187-188.5°C

NMR (CDCl₃, δ) : 1.06 (3H, t, J=7Hz), 1.81 (2H,
sex, J=7Hz), 2.78 (3H, s), 2.93 (2H, t, J=7Hz),
7.32-7.45 (4H, m), 7.69 (1H, d, J=8Hz), 7.82
(1H, br s), 8.35 (1H, d, J=8Hz)

30

Example 1 (36)

3-Benzoyl-7-(2,6-dichlorobenzoylamino)-2-
methylbenzo[b]furan

mp : 213-215°C

35 NMR (CDCl₃, δ) : 2.57 (3H, s), 7.15 (1H, d,

- 103 -

J=8Hz), 7.25 (1H, t, J=8Hz), 7.30-7.45 (3H, m),
7.50 (2H, t, J=8Hz), 7.61 (1H, t, J=8Hz), 7.80-
7.90 (3H, m), 8.31 (1H, d, J=8Hz)

5 Example 1 (37)

7-(2,6-Dichlorobenzoylamino)-3-(1-
ethoxycarbonyl)hydroxymethyl-2-methylbenzo[b]furan

mp : 169-171°C

10 NMR (CDCl₃, δ) : 1.22 (3H, t, J=8Hz), 2.50 (3H,
s), 3.41 (1H, d, J=4Hz), 4.23 (2H, m), 5.30 (1H,
d, J=4Hz), 7.20-7.45 (5H, m), 7.80 (1H, s), 8.28
(1H, d, J=8Hz)

Example 1 (38)

15 3-Cyclohexylcarbonyl-7-(2,6-dichlorobenzoylamino)-2-
methylbenzo[b]furan

mp : 210-211°C

20 NMR (CDCl₃, δ) : 1.20-1.60 (5H, m), 1.60-2.05
(5H, m), 2.78 (3H, s), 3.09 (1H, m), 7.30-7.50
(4H, m), 7.60 (1H, d, J=8Hz), 7.85 (1H, br s),
8.36 (1H, d, J=8Hz)

Example 1 (39)

25 7-(2,6-Dichlorobenzoylamino)-2,3-dihydro-2-
methylbenzo[b]furan

mp : 119-120°C

30 NMR (CDCl₃, δ) : 1.47 (3H, d, J=7Hz), 2.88 (1H,
dd, J=8 and 15Hz), 3.66 (1H, dd, J=8 and 15Hz),
4.99 (1H, m), 6.90 (1H, t, J=8Hz), 6.97 (1H, d,
J=8Hz), 7.25-7.40 (3H, m), 7.48 (1H, br s), 8.25
(1H, d, J=8Hz)

Example 1 (40)

35 7-(2-Chloro-6-fluorobenzoylamino)-2,3-
dimethylbenzo[b]furan

- 104 -

mp : 161-162°C

NMR (CDCl₃, δ) : 2.15 (3H, s), 2.37 (3H, s), 7.12
(1H, t, J=8Hz), 7.20-7.30 (3H, m), 7.39 (1H, m),
7.88 (1H, br s), 8.27 (1H, m)

5

Example 1 (41)

3-Acetyl-7-(2-bromo-6-methylbenzoylamino)-2-methylbenzo[b]furan

mp : 198°C

10

NMR (CDCl₃, δ) : 2.49 (3H, s), 2.67 (3H, s), 2.78
(3H, s), 7.2-7.3 (2H, m), 7.38 (1H, t, J=7.5Hz),
7.48 (1H, dd, J=2 and 7.5Hz), 7.71 (1H, d,
J=7.5Hz), 7.77 (1H, br s), 8.35 (1H, d, J=7.5Hz)

15

Example 1 (42)

7-(2-Chloro-6-methoxybenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 148.5-150°C

20

NMR (CDCl₃, δ) : 1.70 (6H, s), 1.78 (1H, s), 2.57
(3H, s), 3.84 (3H, s), 6.90 (1H, d, J=8Hz), 7.06
(1H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.32 (1H,
t, J=8Hz), 7.42 (1H, d, J=8Hz), 7.87 (1H, br s),
8.32 (1H, d, J=8Hz)

25

Example 1 (43)

3-(1-Hydroxy-1-methylethyl)-2-methyl-7-(6-methyl-2-nitrobenzoylamino)benzo[b]furan

mp : 180-182.5°C

30

NMR (CDCl₃, δ) : 1.71 (6H, s), 1.80 (1H, s), 2.56
(6H, s), 7.23 (1H, t, J=8Hz), 7.48 (1H, d,
J=8Hz), 7.52 (1H, t, J=8Hz), 7.61 (1H, d,
J=8Hz), 7.74 (1H, br s), 8.09 (1H, d, J=8Hz),
8.22 (1H, d, J=8Hz)

35

Example 1 (44)

- 105 -

7-(2-Chloro-6-phenylbenzoylamino)-2,3-
dimethylbenzo[b]furan

mp : 118-120°C

5 NMR (CDCl₃, δ) : 2.09 (3H, s), 2.29 (3H, s),
7.10-7.14 (2H, m), 7.22-7.40 (4H, m), 7.40-7.47
(2H, m), 7.47-7.55 (3H, m), 7.99 (1H, m)

Example 1 (45)

10 3-Acetyl-7-(2,6-dichloro-3-nitrobenzoylamino)-2-
methylbenzo[b]furan

mp : >250°C

15 NMR (DMSO-d₆, δ) : 2.62 (3H, m), 2.80 (3H, m),
7.37 (1H, t, J=8Hz), 7.85 (1H, d, J=8Hz), 7.89
(1H, d, J=8Hz), 7.94 (1H, d, J=8Hz), 8.22 (1H,
d, J=8Hz)

Example 1 (46)

7-(2,6-Dichloro-3-nitrobenzoylamino)-2,3-
dimethylbenzo[b]furan

20 mp : 225-226°C

NMR (CDCl₃, δ) : 2.17 (3H, s), 2.38 (3H, s),
7.21-7.28 (2H, m), 7.57 (1H, d, J=8Hz), 7.85
(1H, br s), 7.90 (1H, br s), 8.22 (1H, m)

25 Example 1 (47)

2,3-Dimethyl-7-(2,4,6-trichlorobenzoylamino)benzo-
[b]furan

mp : 215-217°C

30 NMR (CDCl₃, δ) : 2.16 (3H, s), 2.38 (3H, s),
7.20-7.27 (2H, m), 7.41 (2H, s), 7.79 (1H, br
s), 8.23 (1H, m)

Example 1 (48)

35 7-(2,6-Dichloro-3-methylbenzoylamino)-2,3-
dimethylbenzo[b]furan

- 106 -

mp : 188-190°C

NMR (CDCl₃, δ) : 2.14 (3H, s), 2.35 (3H, s), 2.40
(3H, s), 7.20-7.30 (4H, m), 7.80 (1H, br s),
8.30 (1H, d, J=8Hz)

5

Example 1 (49)

7-(2,6-Dichloro-3-triisopropylsilyloxybenzoyl-
amino)-2,3-dimethylbenzo[b]furan

NMR (CDCl₃, δ) : 1.12 (18H, d, J=7Hz), 1.26-1.39
(3H, m), 2.14 (3H, s), 2.37 (3H, s), 6.90 (1H,
d, J=8Hz), 7.19-7.27 (3H, m), 7.77 (1H, br s),
8.29 (1H, d, J=8Hz)

10

Example 1 (50)

2,3-Dimethyl-7-(2,4,6-triisopropylbenzoylamino)-
benzo[b]furan

mp : 136-137°C

NMR (CDCl₃, δ) : 1.28 (18H, d, J=7.5Hz), 2.14
(3H, s), 2.33 (3H, s), 2.94 (1H, m), 3.14 (2H,
m), 7.10 (2H, s), 7.20 (1H, t, J=7.5Hz), 7.23
(1H, d, J=7.5Hz), 7.84 (1H, br s), 8.31 (1H, d,
J=7.5Hz)

20

Example 1 (51)

7-(2,6-Dichloro-3-dimethylaminomethylbenzoyl-
amino)-2,3-dimethylbenzo[b]furan hydrochloride

mp : >250°C

NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.15 (3H, s), 2.38
(9H, s), 4.42 (2H, s), 7.23 (2H, m), 7.54 (1H,
d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.12 (1H, m)

30

Example 1 (52)

2,3-Dimethyl-7-(2,4,6-trimethylbenzoylamino)-
benzo[b]furan

mp : 151-152°C

35

- 107 -

NMR (CDCl₃, δ) : 2.15 (3H, s), 2.33 (3H, s), 2.34 (3H, s), 2.39 (6H, s), 6.93 (2H, s), 7.1-7.3 (2H, m), 7.75 (1H, br s), 8.29 (1H, d, J=7.5Hz)

5 Example 1 (53)

7-[2,6-Dichloro-3-(2-methoxyethyl)oxymethoxy-methylbenzoylamino]-2,3-dimethylbenzo[b]furan

10 NMR (CDCl₃, δ) : 2.15 (3H, s), 2.37 (3H, s), 3.40 (3H, s), 3.55-3.60 (2H, m), 3.72-3.78 (2H, m), 4.72 (2H, s), 4.87 (2H, s), 7.20-7.28 (2H, m), 7.40 (1H, d, J=8Hz), 7.54 (1H, d, J=8Hz), 7.89 (1H, br s), 8.29 (1H, d, J=8Hz)

Example 1 (54)

15 2,3-Dimethyl-7-(2-iodobenzoylamino)benzo[b]furan

mp : 171-172.5°C

20 NMR (CDCl₃, δ) : 2.16 (3H, s), 2.37 (3H, s), 7.13-7.27 (3H, m), 7.46 (1H, t, J=8Hz), 7.59 (1H, d, J=8Hz), 7.89 (1H, br s), 7.95 (1H, d, J=8Hz), 8.25 (1H, d, J=8Hz)

FAB-Mass (m/z) = 392 (M⁺+1)

Example 1 (55)

25 7-(2-Cyclohexylbenzoylamino)-2,3-dimethylbenzo[b]furan

mp : 137-138°C

30 NMR (CDCl₃, δ) : 1.2-1.6 (5H, m), 1.65-1.85 (3H, m), 1.90-2.00 (2H, m), 2.15 (3H, s), 2.35 (3H, s), 3.07 (1H, m), 7.1-7.4 (3H, m), 7.4-7.5 (2H, m), 7.53 (1H, d, J=7.5Hz), 7.87 (1H, br s), 8.25 (1H, d, J=7.5Hz)

Example 1 (56)

35 2,3-Dimethyl-7-(2,3,5,6-tetramethylbenzoylamino)-benzo[b]furan

- 108 -

mp : 195°C

NMR (CDCl₃, δ) : 2.15 (3H, s), 2.26 (6H, s), 2.29
(6H, s), 2.39 (3H, s), 7.04 (1H, s), 7.1-7.3
(2H, m), 7.78 (1H, br s), 8.33 (1H, d, J=7.5Hz)

5

Example 1 (57)

2,3-Dimethyl-7-(2-methoxy-1-naphthoylamino)-
benzo[b]furan

mp : 165-167°C

10 NMR (CDCl₃, δ) : 2.15 (3H, s), 2.32 (3H, s), 4.01
(3H, s), 7.20 (1H, d, J=8Hz), 7.28 (1H, t,
J=8Hz), 7.33 (2H, d, J=8Hz), 7.40 (1H, t,
J=8Hz), 7.82 (1H, d, J=8Hz), 7.96 (1H, d,
J=8Hz), 8.12 (1H, d, J=8Hz), 8.24 (1H, br s),
15 8.43 (1H, d, J=8Hz)

Example 1 (58)

7-(3,5-Dichloroisonicotinoylamino)-3-(1-hydroxy-1-
methylethyl)-2-methylbenzo[b]furan

20 mp : 170-171.5°C

NMR (CDCl₃, δ) : 1.72 (6H, s), 1.85 (1H, s), 2.60
(3H, s), 7.23 (1H, t, J=8Hz), 7.52 (1H, d,
J=8Hz), 7.86 (1H, br s), 8.21 (1H, d, J=8Hz),
25 8.62 (2H, s)

Example 1 (59)

4-(2,6-Dichlorobenzoylamino)-2,3-dimethylbenzo-
[b]furan

mp : 252-253°C

30 NMR (DMSO-d₆, δ) : 2.31 (3H, s), 2.37 (3H, s),
7.18-7.30 (2H, m), 7.38 (1H, d, J=7Hz), 7.52
(1H, dd, J=7 and 8Hz), 7.55-7.66 (2H, m)

Example 1 (60)

35 6-(2,6-Dichlorobenzoylamino)-2,3-dimethylbenzo-

- 109 -

[b]furan

mp : 175-176°C

NMR (CDCl₃, δ) : 2.15 (3H, s), 2.38 (3H, s),
7.20-7.40 (5H, m), 7.48 (1H, s), 7.90 (1H, s)

5

Example 1 (61)5-(2,6-Dichlorobenzoylamino)-2,3-dimethylbenzo-
[b]furan

mp : 229-230°C

10 NMR (CDCl₃, δ) : 2.17 (3H, s), 2.39 (3H, s),
7.10-7.50 (6H, m), 7.89 (1H, s)Example 1 (62)15 3-(2-Acetylaminothiazol-4-yl)-7-(2,6-
dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : >250°C

20 NMR (CDCl₃:CD₃OD = 1:1, δ) : 2.28 (3H, s), 2.68
(3H, s), 7.05 (1H, s), 7.30 (1H, t, J=7Hz),
7.35-7.50 (3H, m), 7.62 (1H, d, J=7Hz), 8.16
(1H, d, J=7Hz)Example 1 (63)6-Acetyl-1-(2,6-dichlorobenzoylamino)-6,7,8,9-
tetrahydro-5H-10-oxo-6-aza-benzo[b]azulene

25 mp : 252-255°C

NMR (CDCl₃, δ) : 2.00-2.17 (5H, m), 2.97-3.08
(2H, m), 3.72-3.88 (2H m), 4.56 (4/3H, s), 4.77
(2/3H, s), 7.20-7.43 (5H, m), 7.76-7.84 (1H, m),
8.25-8.35 (1H, m)

30

Example 1 (64)7-(2-Chloronicotinoylamino)-3-(1-hydroxy-1-
methylethyl)-2-methylbenzo[b]furan

mp : 92-94°C

35 NMR (CDCl₃, δ) : 1.71 (6H, s), 1.86 (1H, s), 2.60

- 110 -

(3H, s), 7.25 (1H, t, J=8Hz), 7.43 (1H, m), 7.50
(1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.29 (1H,
d, J=8Hz), 8.54 (1H, m), 8.70 (1H, br s)

5 Example 1 (65)

7-(3,5-Dimethyl-2-oxo-2H-pyran-4-yl)carbonylamino-3-
(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

NMR (CDCl₃, δ) : 1.72 (6H, s), 1.87 (1H, s), 2.26
 (3H, s), 2.42 (3H, s), 2.60 (3H, s), 6.08 (1H,
10 s), 7.21 (1H, t, J=8Hz), 7.51 (1H, d, J=8Hz),
 7.86 (1H, br s), 8.08 (1H, d, J=8Hz)

Example 1 (66)

3-(1-Hydroxy-1-methylethyl)-2-methyl-7-(2-
15 trifluoromethylbenzoylamino)benzo[b]furan

mp : 165-166°C

NMR (CDCl₃, δ) : 1.17 (6H, s), 1.80 (1H, s), 2.57
 (3H, s), 7.21 (1H, t, J=8Hz), 7.47 (1H, d,
 J=8Hz), 7.60-7.82 (4H, m), 7.90 (1H, br s), 8.22
20 (1H, d, J=8Hz)

Example 1 (67)

7-(2-Benzoylbenzoylamino)-2,3-dimethylbenzo[b]furan

mp : 219-221.5°C

NMR (CDCl₃, δ) : 2.10 (3H, s), 2.35 (3H, s), 5.38
25 (1H, br s), 6.26 (1H, d, J=8Hz), 6.79 (1H, t,
 J=8Hz), 6.88 (1H, d, J=8Hz), 7.30-7.41 (3H, m),
 7.55 (1H, m), 7.61-7.68 (2H, m), 7.74 (2H, d,
 J=8Hz), 7.91 (1H, d, J=8Hz)

30 Example 1 (68)

2,3-Dimethyl-7-(3,5-dimethylisoxazol-4-yl)-
carbonylaminobenzo[b]furan

NMR (CDCl₃, δ) : 2.16 (3H, s), 2.40 (3H, s), 2.59
35 (3H, s), 2.73 (3H, s), 7.18-7.21 (2H, m), 7.77

- 111 -

(1H, br s), 8.09 (1H, m)

Example 1 (69)

5 7-(3-Chlorobenzo[b]thiophen-2-yl)carbonylamino-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 191-193°C

10 NMR (CDCl₃, δ) : 1.74 (6H, s), 1.86 (1H, s), 2.65 (3H, s), 7.22 (1H, t, J=8Hz), 7.48 (1H, d, J=8Hz), 7.55 (2H, m), 7.89 (1H, dd, J=1.5 and 8Hz), 7.95 (1H, dd, J=1.5 and 8Hz), 8.24 (1H, d, J=8Hz), 9.50 (1H, br s)

Example 1 (70)

15 7-(3-Bromo-1-methylindol-2-yl)carbonylamino-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 154-155°C

20 NMR (CDCl₃, δ) : 1.73 (6H, s), 1.81 (1H, s), 2.62 (3H, s), 4.11 (3H, s), 7.19-7.30 (2H, m), 7.42 (2H, d, J=5Hz), 7.48 (1H, d, J=8Hz), 7.68 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz), 9.03 (1H, br s)

Example 1 (71)

25 7-(6-Benzyloxy-2-chlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 161-162°C

30 NMR (CDCl₃, δ) : 1.71 (6H, s), 1.82 (1H, s), 2.52 (3H, s), 5.18 (2H, s), 6.91 (1H, d, J=8Hz), 7.07 (1H, d, J=8Hz), 7.19-7.31 (5H, m), 7.33-7.40 (2H, m), 7.43 (1H, d, J=8Hz), 7.90 (1H, br s), 8.30 (1H, d, J=8Hz)

Example 1 (72)

35 7-(2-Chloro-6-phenoxybenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 161-162°C

- 112 -

5 NMR (CDCl₃, δ) : 1.70 (6H, s), 1.79 (1H, s), 2.54
(3H, s), 6.82 (1H, d, J=8Hz), 7.06 (2H, d,
J=8Hz), 7.10-7.23 (3H, m), 7.23-7.38 (3H, m),
7.41 (1H, d, J=8Hz), 7.98 (1H, br s), 8.23 (1H,
d, J=8Hz)

Example 1 (73)

7-(2,6-Dichlorobenzoylamino)-3-ethoxycarbonylmethyl-
2-methylbenzo[b]furan
10 mp : 175-177°C
NMR (CDCl₃, δ) : 1.26 (3H, t, J=7Hz), 2.43 (3H,
s), 3.60 (2H, s), 4.16 (2H, q, J=7Hz), 7.23-7.30
(2H, m), 7.30-7.43 (3H, m), 7.80 (1H, br s),
8.30 (1H, d, J=8Hz)

15

Example 1 (74)

3-Bromo-7-(2,6-dichlorobenzoylamino)-2-(2-
ethoxycarbonylethyl)benzo[b]furan
mp : 168-170°C
20 NMR (CDCl₃, δ) : 1.23 (3H, t, J=7Hz), 2.75 (2H,
t, J=7Hz), 3.17 (2H, t, J=7Hz), 4.13 (2H, q,
J=7Hz), 7.25-7.43 (5H, m), 7.77 (1H, m), 8.34
(1H, d, J=8Hz)

25 Example 1 (75)

7-(2,6-Dichlorobenzenesulfonylamino)-3-(1-hydroxy-1-
methylethyl)-2-methylbenzo[b]furan
mp : 166-168°C
30 NMR (CDCl₃, δ) : 1.67 (6H, s), 1.73 (1H, s), 2.51
(3H, s), 7.08 (1H, t, J=8Hz), 7.25 (1H, m), 7.30
(1H, t, J=8Hz), 7.40 (3H, d, J=8Hz), 7.73 (1H,
br s)

Example 1 (76)

35 7-(2,6-Dichlorobenzoyloxy)-2,3-dimethylbenzo[b]furan

- 113 -

mp : 129-130°C

NMR (CDCl₃, δ) : 2.16 (3H, s), 2.39 (3H, s),
7.10-7.25 (2H, m), 7.30-7.45 (4H, m)5 Example 2 (1)

A mixture of 7-carboxy-2,3-dimethylbenzo[b]furan (190 mg) and a catalytic amount of dimethylformamide in thionylchloride (10 ml) was refluxed for 3 hours. After evaporation in vacuo with toluene, it was added to a mixture of 2,6-dichloroaniline (162 mg) and triethylamine (202 mg) in 1,2-dichloroethane (3 ml) at ambient temperature. The mixture was stirred at 60°C for 3 hours and washed with water and brine. After drying over sodium sulfate, it was evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with (CH₂Cl₂:n-hexane = 2:1) and the obtained oil was crystallized from ethanol to give 7-[N-(2,6-dichlorophenyl)carbamoyl]-2,3-dimethylbenzo[b]furan (124 mg).

20 mp : 188-190°C

NMR (CDCl₃, δ) : 2.22 (3H, s), 2.49 (3H, s), 7.23 (1H, t, J=8Hz), 7.36 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz), 9.11 (1H, br s)

25

The following compounds [Examples 2 (2) to (12)] were obtained according to a similar manner to that of Example 2 (1).

30 Example 2 (2)

6-[N-(2,6-Dichlorophenyl)carbamoyl]-1,2,3,4-tetrahydrodibenzofuran

mp : 129°C

NMR (CDCl₃, δ) : 1.80 (2H, m), 2.01 (2H, m), 2.68 (2H, m), 2.83 (2H, m), 7.23 (1H, t, J=7.5Hz),

35

- 114 -

7.36 (1H, t, J=7.5Hz), 7.44 (2H, d, J=7.5Hz),
7.62 (1H, d, J=7.5Hz), 8.12 (1H, d, J=7.5Hz),
9.13 (1H, br s)

5 Example 2 (3)

7-[N-(2-Chloro-6-methylphenyl)carbamoyl]-2,3-
dimethylbenzo[b]furan

mp : 157-158°C

10 NMR (CDCl₃, δ) : 2.22 (3H, s), 2.39 (3H, s), 2.49
(3H, s), 7.18 (1H, t, J=7.5Hz), 7.23 (1H, d,
J=7.5Hz), 7.35 (1H, d, J=7.5Hz), 7.36 (1H, t,
J=7.5Hz), 7.62 (1H, d, J=7.5Hz), 8.11 (1H, d,
J=7.5Hz), 9.02 (1H, br s)

15 Example 2 (4)

7-[N-(2,6-Diisopropylphenyl)carbamoyl]-2,3-
dimethylbenzo[b]furan

mp : 158-159°C

20 NMR (CDCl₃, δ) : 1.23 (12H, d, J=7.5Hz), 2.23
(3H, s), 2.45 (3H, s), 3.23 (2H, m), 7.25 (2H,
d, J=7.5Hz), 7.35 (1H, t, J=7.5Hz), 7.36 (1H, t,
J=7.5Hz), 7.62 (1H, d, J=7.5Hz), 8.12 (1H, d,
J=7.5Hz), 8.73 (1H, br s)

25 Example 2 (5)

2,3-Dimethyl-7-[N-(6-methyl-2-nitrophenyl)-
carbamoyl]benzo[b]furan

mp : 159-160°C

30 NMR (CDCl₃, δ) : 2.23 (3H, s), 2.45 (3H, s), 2.54
(3H, s), 7.30-7.40 (2H, m), 7.58 (1H, d,
J=7.5Hz), 7.63 (1H, d, J=7.5Hz), 7.87 (1H, d,
J=7.5Hz), 8.06 (1H, d, J=7.5Hz), 10.28 (1H, br
s)

35 Example 2 (6)

- 115 -

7-[N-(2,6-Dibromophenyl)carbamoyl]-2,3-
dimethylbenzo[b]furan

mp : 209-210°C

5 NMR (CDCl₃, δ) : 2.22 (3H, s), 2.49 (3H, s), 7.09
(1H, t, J=7.5Hz), 7.37 (1H, t, J=7.5Hz), 7.63
(1H, d, J=7.5Hz), 7.67 (2H, d, J=7.5Hz), 8.13
(1H, d, J=7.5Hz), 9.15 (1H, br s)

Example 2 (7)

10 2,3-Dimethyl-7-[N-(2-methoxy-6-
methylphenyl)carbamoyl]benzo[b]furan

mp : 143-144°C

15 NMR (CDCl₃, δ) : 2.20 (3H, s), 2.35 (3H, s), 2.46
(3H, s), 3.83 (3H, s), 6.82 (1H, d, J=7.5Hz),
6.92 (1H, d, J=7.5Hz), 7.19 (1H, t, J=7.5Hz),
7.34 (1H, t, J=7.5Hz), 7.58 (1H, d, J=7.5Hz),
8.09 (1H, d, J=7.5Hz), 8.87 (1H, br s)

Example 2 (8)

20 7-[N-(6-Chloro-2-methoxycarbonyl)carbamoyl]-2,3-
dimethylbenzo[b]furan

mp : 132-133°C

25 NMR (CDCl₃, δ) : 2.22 (3H, s), 2.51 (3H, s), 3.85
(3H, s), 7.25 (1H, t, J=7.5Hz), 7.34 (1H, t,
J=7.5Hz), 7.62 (1H, d, J=7.5Hz), 7.65 (1H, d,
J=7.5Hz), 7.81 (1H, d, J=7.5Hz), 8.08 (1H, d,
J=7.5Hz)

Example 2 (9)

30 7-[N-(2,4,6-Trichlorophenyl)carbamoyl]-2,3-
dimethylbenzo[b]furan

mp : 189-190°C

35 NMR (CDCl₃, δ) : 2.20 (3H, s), 2.48 (3H, s), 7.36
(1H, t, J=7.5Hz), 7.47 (2H, s), 7.13 (1H, d,
J=7.5Hz), 8.10 (1H, d, J=7.5Hz), 9.03 (1H, br s)

- 116 -

Example 2 (10)

7-[N-(2,6-Dichloro-3-methylphenyl)carbamoyl]-2,3-dimethylbenzo[b]furan

mp : 216-217°C

5 NMR (CDCl₃, δ) : 2.19 (3H, s), 2.40 (3H, s), 2.45 (3H, s), 7.35 (1H, t, J=7.5Hz), 7.40 (1H, d, J=7.5Hz), 7.50 (1H, d, J=7.5Hz), 7.72 (1H, d, J=7.5Hz), 7.73 (1H, d, J=7.5Hz)

10 Example 2 (11)

2,3-Dimethyl-7-[N-(2,4,6-trimethylphenyl)carbamoyl]benzo[b]furan

mp : 149°C

15 NMR (CDCl₃, δ) : 2.21 (3H, s), 2.30 (6H, s), 2.32 (3H, s), 2.45 (3H, s), 6.98 (2H, s), 7.35 (1H, t, J=7.5Hz), 7.60 (1H, d, J=7.5Hz), 8.10 (1H, d, J=7.5Hz), 8.74 (1H, br s)

Example 2 (12)

20 2,3-Dimethyl-7-(N-methoxy-N-methyl)carbamoylbenzo[b]furan

NMR (CDCl₃, δ) : 2.15 (3H, s), 2.40 (3H, s), 3.37 (3H, s), 3.63 (3H, s), 7.21 (1H, t, J=8Hz), 7.34 (1H, d, J=8Hz), 7.47 (1H, d, J=8Hz)

25

Example 3

Lithium aluminium hydride (38 mg) was added to a solution of 2,3-dimethyl 7-(N-methoxy-N-methyl)carbamoylbenzo[b]furan (189 mg) in diethyl ether at 30 4°C. The mixture was stirred at 4°C for 10 minutes, quenched with aqueous 10% tartaric acid and partitioned between diethyl ether and water. The organic layer was separated, washed with water, dried over sodium sulfate and evaporated in vacuo. The residue was dissolved in 35 tetrahydrofuran (5 ml) and added dropwise at 4°C to a

- 117 -

mixture at (2,6-dichlorobenzyl)triphenylphosphonium bromide (407 mg) and potassium tert-butoxide (100 mg) in tetrahydrofuran (5 ml) which was previously stirred at ambient temperature for 30 minutes. The mixture was stirred at ambient temperature for 30 minutes and partitioned between diethyl ether and aqueous saturated sodium bicarbonate. The organic layer was separated, washed with water, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of ethyl acetate and n-hexane to give 7-[2-(2,6-dichlorophenyl)ethenyl]-2,3-dimethylbenzo[b]furan.

mp : 93-94°C

NMR (CDCl₃, δ) : 2.18 (3H, s), 2.44 (3H, s), 7.11 (1H, t, J=7.5Hz), 7.21 (1H, t, J=7.5Hz), 7.30-7.40 (4H, m), 7.40 (1H, d, J=16Hz), 7.63 (1H, d, J=16Hz)

Example 4 (1)

A mixture of 7-amino-2,3-dimethylbenzo[b]furan (100 mg) and 6-chloro-N-methylisatoic anhydride (147 mg) in acetic acid (2 ml) was stirred at 60°C for 2 hours. The reaction mixture was concentrated in vacuo and the residue was crystallized from a mixture of ethanol and water to give 2,3-dimethyl-7-(2-chloro-6-methylaminobenzoylamino)-benzo[b]furan (210 mg).

mp : 175-178°C

NMR (CDCl₃, δ) : 2.14 (3H, s), 2.37 (3H, s), 2.83 (3H, d, J=6Hz), 5.62 (1H, m), 6.59 (1H, d, J=8Hz), 6.73 (1H d, J=8Hz), 7.19 (3H, m), 8.16-8.22 (2H, m)

The following compound was obtained according to a similar manner to that of Example 4 (1).

- 118 -

Example 4 (2)

3-Acetyl-7-(6-amino-2-chlorobenzoylamino)-2-methylbenzo[b]furan

mp : 174-175°C

5 NMR (CDCl₃, δ) : 2.66 (3H, s), 2.80 (3H, s),
4.60-4.97 (2H, m), 6.67 (1H, d, J=7.5Hz), 6.83
(1H, d, J=7.5Hz), 7.15 (1H, t, J=7.5Hz), 7.37
(1H, t, J=7.5Hz), 7.71 (1H, d, J=7.5Hz), 8.25
(1H, br s), 8.30 (1H, d, J=7.5Hz)

10

Example 5 (1)

A mixture of 7-amino-2,3-dimethylbenzo[b]furan (161 mg), triethylamine (202 mg) and 3,6-dichlorophthalic anhydride (261 mg) in dichloromethane (5 ml) was stirred
15 at ambient temperature for 1 hour. The reaction mixture was washed with 1N-hydrochloric acid and brine, dried over sodium sulfate and concentrated in vacuo. The residue was dissolved in methanol and treated with diazomethane. The separated solid was collected and washed with methanol to
20 give 7-(3,6-dichlorophthalimido)-2,3-dimethylbenzo[b]furan (250 mg).

mp : 211-212°C

NMR (CDCl₃, δ) : 2.18 (3H, s), 2.35 (3H, s), 7.14
(1H, d, J=8Hz), 7.30 (1H, t, J=8Hz), 7.49 (1H,
25 d, J=8Hz), 7.65 (2H, s)

FAB-Mass : (m/z) = 360 (M⁺+1)

The following compound was obtained according to a similar manner to that of Example 5 (1).

30

Example 5 (2)

3-(1-Hydroxy-1-methylethyl)-2-methyl-7-(3-nitrophthalimido)benzo[b]furan

mp : 133-136°C

35 NMR (CDCl₃, δ) : 1.72 (6H, s), 1.81 (1H, s), 2.52

- 119 -

(3H, s), 7.17 (1H, d, J=8Hz), 7.30 (1H, t, J=8Hz), 7.82 (1H, d, J=8Hz), 8.00 (1H, t, J=8Hz), 8.20 (1H, d, J=8Hz), 8.26 (1H, d, J=8Hz)

5 Example 6

A solution of 7-(3,6-dichlorophthalimido)-2,3-dimethylbenzo[b]furan (100 mg) in 2N-ammonia in methanol was stirred at ambient temperature for 3 hours. The separated solid was washed with water and dried to give 7-(2,5-dichloro-6-carbamoylbenzoylamino)-2,3-dimethylbenzo[b]furan (63 mg).

mp : 229-232°C

NMR (DMSO-d₆, δ) : 2.14 (3H, s), 2.29 (3H, s),
7.18 (1H, t, J=8Hz), 7.27 (1H, d, J=8Hz), 7.61
15 (2H, s), 7.75-7.85 (3H, m)

Example 7

A solution of 7-(3,6-dichlorophthalimido)-2,3-dimethylbenzo[b]furan (100 mg) in a mixture of aqueous 1N-sodium hydroxide (2 ml) and methanol (3 ml) was stirred at
20 ambient temperature overnight. The reaction mixture was acidified with 1N-hydrochloric acid. The separated solid was collected, washed with water and dried to give 7-(6-carboxy-2,5-dichlorobenzoylamino)-2,3-dimethylbenzo[b]-
25 furan (60 mg).

mp : 186-188°C

NMR (DMSO-d₆, δ) : 2.14 (3H, s), 2.39 (3H, s),
7.19 (1H, t, J=8Hz), 7.28 (1H, d, J=8Hz), 7.66
30 (2H, s), 7.73 (1H, d, J=8Hz)

Example 8

A mixture of 7-amino-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan (150 mg), 3-nitrophthalic anhydride (205 mg) and potassium carbonate (202 mg) in N,N-dimethylformamide (2 ml) was stirred at ambient
35

- 120 -

temperature for 2 hours. Then, isopropyl iodide (280 mg) was added to the mixture and the mixture was stirred for 3 hours. The mixture was partitioned between ethyl acetate and brine. The organic layer was separated, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of 2-propanol and water to give 3-(1-hydroxy-1-methylethyl)-7-(6-isopropoxycarbonyl-2-nitrobenzoylamino)-2-methylbenzo[b]furan (136 mg).

mp : 118-120°C

NMR (CDCl₃, δ) : 1.19 (6H, d, J=7Hz), 1.71 (6H, s), 1.82 (1H, s), 2.54 (3H, s), 5.20 (1H, m), 7.21 (1H, d, J=8Hz), 7.44 (1H, d, J=8Hz), 7.72 (1H, t, J=8Hz), 7.83 (1H, br s), 8.28 (1H, d, J=8Hz), 8.36 (2H, dd, J=1.5 and 8Hz)

Example 9

A mixture of 3-(1-hydroxy-1-methylethyl)-2-methyl-7-(3-nitrophthalimido)benzo[b]furan (80 mg) and sodium borohydride (16 mg) in ethanol (2 ml) was stirred at ambient temperature for 3 hours. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 3-(1-hydroxy-1-methylethyl)-7-(3-hydroxy-4-nitrophthalimidin-2-yl)-2-methylbenzo[b]furan (39 mg).

mp : 156-158°C

NMR (CDCl₃, δ) : 1.72 (6H, s), 1.84 (1H, s), 2.59 (3H, s), 3.77 (1H, d, J=5Hz), 7.24-7.33 (2H, m), 7.53 (1H, d, J=8Hz), 7.71 (1H, d, J=8Hz), 7.81 (1H, d, J=8Hz), 8.29 (1H, d, J=8Hz), 8.44 (1H, d, J=8Hz)

- 121 -

Example 10 (1)

Methanesulfonyl chloride (0.073 ml) was added to a solution of 2,3-dimethyl-7-hydroxymethylbenzo[b]furan (150 mg) and triethylamine (0.166 ml) in dichloromethane at 4°C. The mixture was stirred at 4°C for 35 minutes. The mixture was washed with aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was dissolved in N,N-dimethylformamide and to the solution was added potassium carbonate (248 mg) and 2,6-dichlorophenol (97 mg). The mixture was stirred at 60°C for 2 hours and poured into a mixture of ice and water. The separated oil was extracted with ethyl acetate and the extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by preparative TLC and the obtained oil was crystallized from petroleum ether to give 7-(2,6-dichlorophenoxy)methyl-2,3-dimethylbenzo[b]furan (69 mg).

mp : 87-88°C

NMR (CDCl₃, δ) : 2.15 (3H, s), 2.37 (3H, s), 5.38 (2H, s), 7.00 (1H, t, J=7.5Hz), 7.22 (1H, t, J=7.5Hz), 7.30 (2H, d, J=7.5Hz), 7.40 (1H, d, J=7.5Hz), 7.46 (1H, d, J=7.5Hz)

The following compound was obtained according to a similar manner to that of Example 10 (1).

Example 10 (2)

7-(2,6-Dichlorobenzyloxy)-2,3-dimethylbenzo[b]furan

mp : 108-110°C

NMR (CDCl₃, δ) : 2.13 (3H, s), 2.48 (3H, s), 5.50 (2H, s), 6.90 (1H, d, J=7Hz), 7.05 (1H, d, J=7Hz), 7.12 (1H, t, J=7Hz), 7.22 (1H, t, J=7Hz), 7.35 (2H, d, J=7Hz)

Example 11 (1)

- 122 -

A mixture of 6-amino-1,2,3,4-tetrahydrodibenzofuran (230 mg), 2,5-hexanedione (145 mg) and conc. hydrochloric acid (1 drop) in ethanol (3 ml) was refluxed for 1 hour and poured into water. The mixture was neutralized with aqueous saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of ethanol and water to give 6-(2,5-dimethylpyrrol-1-yl)-1,2,3,4-tetrahydrodibenzofuran (235 mg).

mp : 86-88°C

NMR (CDCl₃, δ) : 1.80-1.99 (4H, m), 2.02 (6H, s), 2.62-2.75 (4H, m), 5.98 (2H, s), 7.07 (1H, d, J=8Hz), 7.27 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz)

The following compound was obtained according to a similar manner to that of Example 11 (1).

Example 11 (2)

6-[2,6-Dichloro-3-(2,5-dimethylpyrrol-1-yl)benzoylamino]-1,2,3,4-tetrahydrodibenzofuran

mp : 244-245°C

NMR (CDCl₃, δ) : 1.79-2.00 (4H, m), 2.02 (6H, s), 2.59-2.80 (4H, m), 5.96 (2H, s), 7.25 (2H, d, J=5Hz), 7.34 (1H, d, J=8Hz), 7.52 (1H, d, J=8Hz), 7.89 (1H, br s), 8.28 (1H, m)

Example 12 (1)

To a solution of 3-acetyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (100 mg) in tetrahydrofuran (3 ml) was added a 1M solution of methylmagnesium bromide in tetrahydrofuran (0.7 ml) dropwise with ice cooling. The solution was stirred at ambient temperature for 2 hours and to the solution was

- 123 -

added aqueous saturated ammonium chloride. Then, the mixture was poured into water and the separated oil was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo.

5 The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of diisopropyl ether and hexane to give 7-(2,6-dichlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan (75 mg).

10 mp : 129-131°C

NMR (CDCl₃, δ) : 1.72 (6H, s), 1.82 (1H, s), 2.59 (3H, s), 7.22 (1H, d, J=7Hz), 7.30-7.50 (4H, m), 7.82 (1H, br s), 8.29 (1H, d, J=7Hz)

15 The following compounds [Examples 12 (2) to (12)] were obtained according to a similar manner to that of Example 12 (1).

Example 12 (2)

20 7-(2,6-Dichlorobenzoylamino)-3-(1-ethyl-1-hydroxypropyl)-2-methylbenzo[b]furan

mp : 139-141°C

25 NMR (CDCl₃, δ) : 0.86 (6H, t, J=7Hz), 1.60 (1H, s), 1.86 (2H, m), 2.08 (2H, m), 2.59 (3H, s), 7.20 (1H, t, J=7Hz), 7.30-7.45 (4H, m), 7.85 (1H, br s), 8.28 (1H, d, J=7Hz)

Example 12 (3)

30 7-(2,6-Dichlorobenzoylamino)-5-fluoro-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 159-161°C

NMR (CDCl₃, δ) : 1.70 (6H, s), 1.79 (1H, s), 2.57 (3H, s), 7.18 (1H, d, J=8Hz), 7.30-7.45 (3H, m), 7.83 (1H, br s), 8.13 (1H, d, J=8Hz)

- 124 -

Example 12 (4)

7-(2-Chloro-6-methylbenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 161-162°C

5 NMR (CDCl₃, δ) : 1.72 (6H, s), 1.80 (1H, s), 2.46 (3H, s), 2.58 (3H, s), 7.17-7.26 (2H, m), 7.29-7.31 (2H, m), 7.47 (1H, d, J=8Hz), 7.80 (1H, br s), 8.29 (1H, d, J=8Hz)

10 Example 12 (5)

7-(2,6-Dichlorobenzoylamino)-3-(3-hydroxy-3-methylbutyl)-2-methylbenzo[b]furan

mp : 171-173°C

15 NMR (CDCl₃, δ) : 1.33 (6H, s), 1.78 (2H, m), 2.39 (3H, s), 2.70 (2H, m), 7.20-7.30 (2H, m), 7.30-7.45 (3H, m), 7.83 (1H, br s), 8.29 (1H, d, J=7Hz)

Example 12 (6)

20 5-Chloro-7-(2,6-dichlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 181-184°C

25 NMR (CDCl₃, δ) : 1.69 (6H, s), 1.80 (1H, s), 2.57 (3H, s), 7.30-7.45 (3H, m), 7.48 (1H, s), 7.80 (1H, br s), 8.35 (1H, s)

Example 12 (7)

7-(3-Acetylamino-2,6-dichlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

30 mp : 136-140°C

NMR (CDCl₃:CD₃OD = 19:1, δ) : 1.70 (6H, s), 2.27 (3H, s), 2.58 (3H, s), 7.22 (1H, t, J=8Hz), 7.39 (1H, d, J=8Hz), 7.50 (1H, d, J=8Hz), 8.11 (2H, d, J=8Hz)

35

- 125 -

Example 12 (8)

7-(2,6-Dichloro-3-dimethylaminoacetyl-amino-benzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

5 mp : 201-203°C

NMR (CDCl₃, δ) : 1.72 (6H, s), 1.82 (1H, s), 2.42 (6H, s), 2.59 (3H, s), 3.14 (2H, s), 7.15-7.30 (2H, m), 7.39 (1H, d, J=8Hz), 7.48 (1H, d, J=8Hz), 7.86 (1H, s), 8.27 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz)

10

Example 12 (9)

7-(2-Bromo-6-methylbenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

15 mp : 173-175°C

NMR (CDCl₃, δ) : 1.71 (6H, s), 2.47 (3H, s), 2.57 (3H, s), 7.1-7.3 (3H, m), 7.4-7.5 (2H, m), 7.77 (1H, br s), 8.27 (1H, d, J=7.5Hz)

20 Example 12 (10)

6-(2,6-Dichlorobenzoylamino)-1-hydroxy-1-methyl-1,2,3,4-tetrahydrodibenzofuran

mp : 180-182°C

NMR (CDCl₃, δ) : 1.72 (3H, s), 1.83 (1H, s), 1.90-2.00 (3H, m), 2.02-2.10 (1H, m), 2.63-2.83 (2H, m), 7.24-7.32 (2H, m), 7.32-7.43 (2H, m), 7.52 (1H, d, J=8Hz), 7.83 (1H, br s), 8.31 (1H, d, J=8Hz)

25

30 Example 12 (11)

6-(2,6-Dichlorobenzoylamino)-9-(1-hydroxy-1-methylethyl)-1,2,3,4-tetrahydrodibenzofuran

mp : 192-194°C

NMR (CDCl₃, δ) : 1.72 (6H, s), 1.80-2.00 (4H, m), 2.75 (2H, m), 2.98 (2H, m), 7.21 (1H, d,

35

- 126 -

J=7Hz), 7.30-7.45 (3H, m), 7.90 (1H, br s), 8.21 (1H, d, J=7Hz)

Example 12 (12)

5 7-(6-Acetylamino-2-chlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 219-220°C

NMR (CDCl₃, δ) : 1.72 (6H, s), 1.84 (1H, s), 2.17 (3H, s), 2.58 (3H, s), 7.20-7.28 (2H, m), 7.41 (1H, t, J=8Hz), 7.53 (1H, d, J=8Hz), 8.13 (1H, d, J=8Hz), 8.22-8.29 (2H, m), 9.02 (1H, br s)

Example 13 (1)

15 Sodium borohydride (7 mg) was added to a solution of 7-(2,6-dichlorobenzoylamino)-3-(1-ethoxycarbonyl)hydroxymethyl-2-methylbenzo[b]furan (76 mg) in methanol (3 ml) at 4°C. The mixture was stirred at ambient temperature for 3 hours and poured into cold water. The separated oil was extracted with ethyl acetate and the extract was washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by colum chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 7-(2,6-dichlorobenzoylamino)-3-(1,2-dihydroxyethyl)-2-methylbenzo[b]furan (35 mg).

mp : 167-168°C

NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.47 (3H, s), 3.71 (1H, dd, J=4 and 11Hz), 3.90 (1H, dd, J=8 and 11Hz), 4.96 (1H, dd, J=4 and 8Hz), 7.22 (1H, t, J=8Hz), 7.30-7.50 (4H, m), 8.15 (1H, d, J=8Hz)

The following compounds [Examples 13 (2) to (7)] were obtained according to a similar manner to that of Example 13 (1).

- 127 -

Example 13 (2)

7-(2,6-Dichlorobenzoylamino)-3-(1-hydroxyethyl)-2-methylbenzo[b]furan

mp : 209-211°C

5 NMR (CDCl₃:CD₃OD = 9:1, δ) : 1.62 (3H, d, J=6Hz),
2.46 (3H, s), 5.11 (1H, q, J=6Hz), 7.25 (1H, t,
J=7Hz), 7.30-7.45 (3H, m), 7.52 (1H, d, J=7Hz),
8.23 (1H, d, J=7Hz)

10 Example 13 (3)

7-(2,6-Dichlorobenzoylamino)-3-(1-hydroxybutyl)-2-methylbenzo[b]furan

mp : 165-166.5°C

15 NMR (CDCl₃, δ) : 0.95 (3H, t, J=7Hz), 1.20-1.48
(2H, m), 1.80 (1H, d, J=2Hz), 1.82-2.09 (2H, m),
2.43 (3H, s), 4.89 (1H, m), 7.25 (1H, m), 7.30-
7.43 (3H, m), 7.48 (1H, d, J=8Hz), 7.80 (1H, br
s), 8.29 (1H, d, J=8Hz)

20 Example 13 (4)

7-(2,6-Dichlorobenzoylamino)-3-(1-hydroxy)phenylmethyl-2-methylbenzo[b]furan

mp : 90-100°C

25 NMR (CDCl₃, δ) : 2.24 (1H, d, J=3Hz), 2.48 (3H,
s), 6.08 (1H, d, J=3Hz), 7.10-7.20 (2H, m),
7.25-7.50 (8H, m), 7.81 (1H, br s), 8.25 (1H,
dd, J=2 and 8Hz)

Example 13 (5)

30 6-(2,6-Dichlorobenzoylamino)-1,2-dihydro-1-hydroxy-
4H-thiopyrano[3,4-b]benzo[b]furan

mp : 214-216°C

35 NMR (CDCl₃, δ) : 2.44 (1H, d, J=10Hz), 2.96 (1H,
dd, J=4 and 14Hz), 3.15 (1H, dd, J=4 and 14Hz),
3.56 (1H, d, J=16Hz), 3.88 (1H, d, J=16Hz), 5.09

- 128 -

(1H, td, J=4 and 10Hz), 7.30-7.45 (4H, m), 7.47 (1H, d, J=8Hz), 7.78 (1H, br s), 8.32 (1H, d, J=8Hz)

5 Example 13 (6)

3-(1-Cyclohexyl)hydroxymethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 214-216°C

10 NMR (CDCl₃, δ) : 0.80-2.20 (12H, m), 2.40 (3H, s), 4.54 (1H, d, J=8Hz), 7.23 (1H, t, J=8Hz), 7.30 (1H, t, J=8Hz), 7.30-7.50 (4H, m), 7.80 (1H, br s), 8.28 (1H, d, J=8Hz)

Example 13 (7)

15 6-(2,6-Dichlorobenzoylamino)-1-hydroxy-1,2,3,4-tetrahydrodibenzofuran

mp : 163-165°C

20 NMR (CDCl₃, δ) : 1.70 (1H, d, J=7Hz), 1.88-1.99 (2H, m), 1.99-2.14 (2H, m), 2.62-2.84 (2H, m), 5.03 (1H, m), 7.23-7.32 (2H, m), 7.32-7.47 (3H, m), 7.82 (1H, br s), 8.30 (1H, d, J=8Hz)

Example 14 (1)

25 A mixture of 7-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-methylbenzo[b]furan (123 mg), acetic anhydride (43 mg) and pyridine (48 mg) in dichloromethane (5 ml) was refluxed for 2 hours. The reaction mixture was washed with 1N-hydrochloric acid, brine and aqueous saturated sodium bicarbonate, dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from diethyl ether to give 3-acetoxymethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (115 mg).

mp : 196-197°C

35 NMR (CDCl₃, δ) : 2.07 (3H, s), 2.50 (3H, s), 5.20 (2H, s), 7.27-7.45 (5H, m), 7.81 (1H, br s),

- 129 -

8.32 (1H, d, J=7Hz)

The following compounds [Examples 14 (2) to (7)] were
obtained according to a similar manner to that of Example
5 14 (1).

Example 14 (2)

3-(1-Acetoxyethyl)-7-(2,6-dichlorobenzoylamino)-2-
methylbenzo[b]furan

10 mp : 180-181°C

NMR (CDCl₃, δ) : 1.17 (3H, d, J=7Hz), 2.04 (3H,
s), 2.48 (3H, s), 6.03 (1H, q, J=7Hz), 7.20-7.43
(4H, m), 7.47 (1H, d, J=8Hz), 7.80 (1H, br s),
8.30 (1H, d, J=8Hz)

15

Example 14 (3)

7-(2,6-Dichlorobenzoylamino)-3-
ethoxycarbonyloxymethyl-2-methylbenzo[b]furan

mp : 178-179°C

20 NMR (CDCl₃, δ) : 1.39 (3H, t, J=7Hz), 2.50 (3H,
s), 4.19 (2H, q, J=7Hz), 5.25 (2H, s), 7.25-7.45
(5H, m), 7.80 (1H, br s), 8.30 (1H, d, J=8Hz)

Example 14 (4)

25 7-(2,6-Dichlorobenzoylamino)-3-
diethoxyphosphoryloxymethyl-2-methylbenzo[b]furan

mp : 149-152°C

NMR (CDCl₃, δ) : 1.28 (6H, t, J=7Hz), 2.50 (3H,
s), 4.06 (4H, quint., J=7Hz), 5.17 (2H, d,
30 J=8Hz), 7.25-7.45 (5H, m), 7.80 (1H, br s), 8.31
(1H, d, J=8Hz)

Example 14 (5)

3-Benzoyloxymethyl-7-(2,6-dichlorobenzoylamino)-2-
35 methylbenzo[b]furan

- 130 -

mp : 191-192°C

NMR (CDCl₃, δ) : 2.55 (3H, s), 5.45 (2H, s),
7.25-7.45 (7H, m), 7.55 (1H, t, J=8Hz), 7.82
(1H, br s), 8.01 (2H, d, J=8Hz), 8.32 (1H, d,
J=8Hz)

5

Example 14 (6)

3-Cyclohexylcarbonyloxymethyl-7-(2,6-
dichlorobenzoylamino)-2-methylbenzo[b]furan

10

mp : 207-209°C

NMR (CDCl₃, δ) : 1.10-1.95 (10H, m), 2.30 (1H,
m), 2.50 (3H, s), 5.19 (2H, s), 7.25-7.45 (5H,
m), 7.81 (1H, br s), 8.30 (1H, d, J=8Hz)

15

Example 14 (7)

3-(4-Carboxybutyryl)oxymethyl-7-(2,6-
dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 150-152°C

20

NMR (CDCl₃:CD₃OD = 9:1, δ) : 1.93 (2H, quint.,
J=7Hz), 2.33 (2H, t, J=7Hz), 2.40 (2H, t,
J=7Hz), 2.50 (3H, s), 5.21 (2H, s), 7.25-7.45
(5H, m), 8.23 (1H, d, J=8Hz)

Example 15

25

A mixture of 3-(4-carboxybutyryl)oxymethyl-7-(2,6-
dichlorobenzoylamino)-2-methylbenzo[b]furan (2.27 g),
disuccinimidyl carbonate (2.51 g) and pyridine (1.16 g) in
acetonitrile (100 ml) was stirred at ambient temperature
for 2 days. The reaction mixture was concentrated in
vacuo and the residue was crystallized from a mixture of
ethyl acetate and hexane to give 7-(2,6-
dichlorobenzoylamino)-2-methyl-3-(4-succinimidyloxy-
carbonylbutyryl)oxymethylbenzo[b]furan (2.6 g).

30

mp : 117-121°C

35

NMR (CDCl₃, δ) : 2.05 (2H, quint., J=7Hz), 2.48

- 131 -

(2H, t, J=7Hz), 2.50 (3H, s), 2.68 (2H, t, J=7Hz), 2.81 (4H, s), 5.22 (2H, s), 7.29 (1H, t, J=8Hz), 7.32-7.45 (4H, m), 7.89 (1H, br s), 8.30 (1H, d, J=8Hz)

5

The following compounds [Examples 16 (1) to (6)] were obtained according to a similar manner to that of Preparation 10.

10 Example 16 (1)

3-(Benzimidazol-2-ylthiomethyl)-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 155°C

15 NMR (CDCl₃, δ) : 2.38 (3H, s), 4.60 (2H, s),
7.18-7.40 (8H, m), 7.70 (1H, d, J=8Hz), 7.80
(1H, br s), 8.28 (1H, d, J=8Hz), 9.18 (1H, br s)

Example 16 (2)

20 7-(2,6-Dichlorobenzoylamino)-3-ethoxycarbonylmethylthiomethyl-2-methylbenzo[b]furan

mp : 118-122°C

25 NMR (CDCl₃, δ) : 1.28 (3H, t, J=8Hz), 2.44 (3H, s), 3.08 (2H, s), 3.92 (2H, s), 4.16 (2H, q, J=8Hz), 7.20-7.45 (5H, m), 7.79 (1H, br s), 8.30
(1H, d, J=8Hz)

Example 16 (3)

30 7-(2,6-Dichlorobenzoylamino)-3-(2-hydroxyethyl)thiomethyl-2-methylbenzo[b]furan

mp : 164-167°C

NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.43 (3H, s), 2.62
(2H, t, J=7Hz), 3.70 (2H, t, J=7Hz), 3.82 (2H, s), 7.27 (1H, t, J=8Hz), 7.30-7.45 (4H, m), 8.12
(1H, d, J=8Hz)

35

- 132 -

Example 16 (4)

7-(2,6-Dichlorobenzoylamino)-3-[(imidazol-1-yl)thiomethyl]-2-methylbenzo[b]furan hydrochloride

mp : 218-221°C

5 NMR (DMSO-d₆, δ) : 2.23 (3H, s), 4.62 (2H, s),
7.25 (1H, t, J=8Hz), 7.41 (1H, d, J=8Hz), 7.47-
7.60 (3H, m), 7.72 (2H, s), 7.82 (1H, d, J=8Hz)

Example 16 (5)

10 7-(2,6-Dichlorobenzoylamino)-3-
(dimethoxyphosphorylmethyl)-2-methylbenzo[b]furan

mp : 215-218°C

NMR (CDCl₃, δ) : 2.43 (3H, d, J=4Hz), 3.12 (2H,
d, J=20Hz), 3.68 (6H, d, J=9Hz), 7.20-7.45 (5H,
15 m), 7.82 (1H, br s), 8.29 (1H, d, J=8Hz)

Example 16 (6)

7-(2,6-Dichlorobenzoylamino)-3-methoxymethyl-2-
methylbenzo[b]furan

20 mp : 199-200°C

NMR (CDCl₃, δ) : 2.45 (3H, s), 3.37 (3H, s), 4.54
(2H, s), 7.2-7.5 (5H, m), 7.81 (1H, br s), 8.30
(1H, d, J=7.5Hz)

25 Example 17

A mixture of 3-chloromethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (150 mg),
imidazole (33 mg) and triethylamine (62 mg) in 1,2-dichloroethane (1.5 ml) was refluxed for 3 hours. The
30 reaction mixture was evaporated in vacuo and the residue
was purified by column chromatography on silica gel. The
obtained oil was crystallized from a mixture of ethyl
acetate and diisopropyl ether and the crystalline was
treated with ethanolic hydrogen chloride. The separated
35 solid was collected and washed with ethanol to give 7-

- 133 -

(2,6-dichlorobenzoylamino)-3-(imidazol-1-yl)methyl-2-methylbenzo[b]furan hydrochloride (62 mg).

mp : >250°C

5 NMR (DMSO-d₆, δ) : 2.61 (3H, s), 5.61 (2H, s),
7.23 (1H, t, J=8Hz), 7.37 (1H, d, J=8Hz), 7.48-
7.60 (3H, m), 7.70 (1H, d, J=3Hz), 7.80 (1H, d,
J=3Hz), 7.83 (1H, d, J=8Hz), 9.30 (1H, s)

Example 18

10 A mixture of 3-bromo-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (165 mg), 2-(tributylstannyl)pyridine (213 mg) and tetrakis(triphenylphosphine)palladium (10 mg) in 1,2-dimethoxyethane (3 ml) was refluxed for 18 hours. The reaction mixture was evaporated in vacuo and the
15 residue was purified by column chromatography on silica gel. The obtained oil was dissolved in methanolic hydrogen chloride and to the solution was evaporated in vacuo. The residue was crystallized from ethyl acetate to give 7-(2,6-dichlorobenzoylamino)-2-methyl-3-(pyridin-2-
20 yl)benzo[b]furan hydrochloride (45 mg).

mp : 240-243°C

25 NMR (DMSO-d₆, δ) : 2.71 (3H, s), 7.32 (1H, t, J=8Hz), 7.49-7.61 (4H, m), 7.71 (1H, d, J=8Hz), 7.85-7.91 (2H, m), 8.15 (1H, m), 8.81 (1H, d, J=5Hz)

Example 19

A solution of 5-(tert-butoxycarbonylamino)-7-(2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan (1.56 g)
30 in 4N-hydrogen chloride in ethyl acetate (10 ml) was stirred at ambient temperature for 1 hour and to the reaction mixture was added diethyl ether. The separated solid was collected, washed with diethyl ether and dried to give 5-amino-7-(2,6-dichlorobenzoylamino)-2,3-
35 dimethylbenzo[b]furan hydrochloride (1.23 g).

- 134 -

mp : >250°C

NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.16 (3H, s), 2.40
(3H, s), 7.30-7.50 (4H, m), 8.12 (1H, s)

5 Example 20

A solution of 3-tert-butoxycarbonylaminomethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (312 mg) in trifluoroacetic acid (2 ml) was stirred at ambient temperature for 10 minutes. The reaction mixture was concentrated in vacuo and to the residue was added aqueous saturated sodium bicarbonate. The separated solid was collected, washed with water and dried to give 3-aminomethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (210 mg).

15 mp : 200-203°C

NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.45 (3H, s), 3.89
(2H, s), 7.18-7.48 (5H, m), 8.22 (1H, d, J=7Hz)

Example 21 (1)

20 A mixture of 5-amino-7-(2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan hydrochloride (116 mg) and acetic anhydride (74 mg) in acetic acid (1 ml) was stirred at 80°C for 1.5 hours. The reaction mixture was cooled and to the mixture was added water. The separated solid was collected, washed with water and dried to give 5-acetylamino-7-(2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan (97 mg).

mp : >250°C

30 NMR (DMSO-d₆, δ) : 2.05 (3H, s), 2.11 (3H, s),
2.38 (3H, s), 7.40-7.60 (3H, m), 7.79 (1H, s),
7.89 (1H, s), 10.00 (1H, s), 10.89 (1H, s)

The following compounds [Examples 21 (2) to (5)] were obtained according to a similar manner to that of Example 21 (1).

- 135 -

Example 21 (2)

3-Acetylaminomethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : >250°C

5 NMR (CDCl₃:CD₃OD = 9:1, δ) : 1.98 (3H, s), 2.47 (3H, s), 4.43 (2H, s), 7.20-7.50 (5H, m), 8.15 (1H, d, J=7Hz)

Example 21 (3)

10 6-(3-Acetyl-amino-2,6-dichlorobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran

mp : >250°C

15 NMR (CDCl₃, δ) : 1.79-2.00 (4H, m), 2.28 (3H, s), 2.58-2.77 (4H, m), 7.20-7.28 (2H, m), 7.39 (1H, d, J=8Hz), 7.66 (1H, br s), 7.88 (1H, br s), 8.28 (1H, dd, J=6 and 6Hz), 8.42 (1H, d, J=8Hz)

Example 21 (4)

20 3-Acetyl-7-(3-acetyl-amino-2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : >250°C

25 NMR (DMSO-d₆, δ) : 2.13 (3H, s), 2.12 (3H, s), 2.79 (3H, s), 7.35 (1H, t, J=8Hz), 7.53 (1H, d, J=8Hz), 7.75-7.90 (3H, m), 9.72 (1H, s)

Example 21 (5)

3-Acetyl-7-(6-acetyl-amino-2-chlorobenzoylamino)-2-methylbenzo[b]furan

mp : 250-252.5°C

30 NMR (CDCl₃:CD₃OD = 20:1, δ) : 2.17 (3H, s), 2.67 (3H, s), 2.80 (3H, s), 7.29 (1H, d, J=8Hz), 7.38 (1H, t, J=8Hz), 7.42 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz)

35

- 136 -

The following compounds [Examples 22 (1) to (4)] were obtained according to a similar manner to that of Preparation 11 (1).

5 Example 22 (1)

3-(2-Carboxyethyl)-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 211-213°C

10 NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.42 (3H, s), 2.67
(2H, t, J=7.5Hz), 2.95 (2H, t, J=7.5Hz), 7.23-
7.29 (2H, m), 7.32-7.43 (3H, m), 8.28 (1H, m)

Example 22 (2)

15 5-Carboxy-7-(2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan

mp : >250°C

NMR (CDCl₃:CD₃OD = 1:1, δ) : 2.20 (3H, s), 2.41 (3H, s), 7.30-7.50 (3H, m), 8.03 (1H, s), 8.68 (1H, s)

20

Example 22 (3)

7-[N-(6-Carboxy-2-chlorophenyl) carbamoyl]-2,3-dimethylbenzo[b]furan

mp : 194-195°C

25 NMR (CDCl₃, δ) : 2.18 (3H, s), 2.43 (3H, s), 7.27
(1H, t, J=7.5Hz), 7.30 (1H, t, J=7.5Hz), 7.59
(1H, d, J=7.5Hz), 7.67 (1H, d, J=7.5Hz), 7.87
(1H, d, J=7.5Hz), 8.07 (1H, d, J=7.5Hz)

30 Example 22 (4)

3-Carboxymethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : >250°C

35 NMR (DMSO-d₆, δ) : 2.40 (3H, s), 3.63 (2H, s), 7.20
(1H, t, J=8Hz), 7.30 (1H, d, J=8Hz), 7.49 (1H,

- 137 -

m), 7.54-7.60 (2H, m), 7.78 (1H, d, J=8Hz)

The following compound was obtained according to a similar manner to that of Preparation 33.

5

Example 23

3-Chloromethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 216-217°C

10 NMR (CDCl₃, δ) : 2.49 (3H, s), 4.70 (2H, s), 7.30 (1H, t, J=8Hz), 7.35-7.43 (4H, m), 7.80 (1H, br s), 8.33 (1H, d, J=8Hz)

Example 24 (1)

15 A mixture of 3-(2-carboxyethyl)-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (90 mg), 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (43 mg) and 1-hydroxybenzotriazole (37 mg) in N,N-dimethylformamide (1 ml) was stirred at ambient temperature for 30 minutes. To
20 the mixture was added dimethylamine hydrochloride (22 mg) and the mixture was stirred for 5 hours. The reaction mixture was poured into cold water and the separated oil was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and concentrated in
25 vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 7-(2,6-dichlorobenzoylamino)-3-(2-N,N-dimethylcarbamoyl-ethyl)-2-methylbenzo[b]furan (67 mg).

30 mp : 163-169°C

NMR (CDCl₃, δ) : 2.42 (3H, s), 2.62 (2H, t, J=7Hz), 2.91 (3H, s), 2.95 (3H, s), 2.98 (2H, t, J=7Hz), 7.23-7.28 (2H, m), 7.31-7.44 (3H, m), 7.83 (1H, br s), 8.30 (1H, m)

35

- 138 -

The following compounds [Examples 24 (2) to (11)] were obtained according to a similar manner to that of Example 24 (1).

5 Example 24 (2)

3-[(N-Cyclopentyl)carbamoylmethyl]-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : 247-248°C

10 NMR (DMSO-d₆, δ) : 1.32-1.58 (4H, m), 1.58-1.85 (4H, m), 2.41 (3H, s), 3.41 (2H, s), 3.99 (1H, m), 7.20 (1H, t, J=8Hz), 7.37 (1H, d, J=8Hz), 7.48 (1H, m), 7.58 (2H, d, J=8Hz), 7.77 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz)

15 Example 24 (3)

7-(2,6-Dichlorobenzoylamino)-2-methyl-3-[[N-(pyridin-2-yl)methyl]carbamoylmethyl]benzo[b]furan hydrochloride

mp : 221-224°C

20 NMR (DMSO-d₆, δ) : 2.44 (3H, s), 3.63 (2H, s), 4.55 (2H, d, J=6Hz), 7.20 (1H, t, J=8Hz), 7.37 (1H, d, J=8Hz), 7.49 (1H, m), 7.58 (2H, d, J=8Hz), 7.68 (1H, d, J=7Hz), 7.72 (1H, m), 7.79 (1H, d, J=8Hz), 8.28 (1H, t, J=7Hz), 8.73 (1H, d, J=7Hz), 8.90 (1H, m)

25

Example 24 (4)

7-(2,6-Dichlorobenzoylamino)-3-[[N-(2-methoxyethyl)carbamoylmethyl]-2-methylbenzo[b]furan

mp : 215-216°C

30 NMR (DMSO-d₆, δ) : 3.18-3.25 (5H, m), 3.35 (2H, t, J=7Hz), 3.47 (2H, s), 7.20 (1H, t, J=8Hz), 7.38 (1H, d, J=8Hz), 7.45-7.60 (3H, m), 7.78 (1H, d, J=8Hz), 8.20 (1H, br t, J=8Hz)

35 Example 24 (5)

- 139 -

7-(2,6-Dichlorobenzoylamino)-3-([N-(2-hydroxyethyl)]carbamoylmethyl)-2-methylbenzo[b]furan

mp : 175-178°C

5 NMR (DMSO-d₆, δ) : 2.42 (3H, m), 3.13 (2H, t, J=7Hz), 3.40 (2H, t, J=7Hz), 3.47 (2H, s), 4.69 (1H, t, J=7Hz), 7.19 (1H, t, J=8Hz), 7.36 (1H, t, J=8Hz), 7.46-7.60 (3H, m), 7.74-7.80 (1H, m)

Example 24 (6)

10 7-(2,6-Dichlorobenzoylamino)-2-methyl-3-[(morpholin-4-yl)carbonylmethyl]benzo[b]furan

mp : 260-261°C

15 NMR (DMSO-d₆, δ) : 2.39 (3H, s), 3.40-3.60 (8H, m), 3.75 (2H, s), 7.18 (1H, t, J=8Hz), 7.29 (1H, d, J=8Hz), 7.40-7.60 (3H, m), 7.77 (1H, d, J=8Hz)

Example 24 (7)

20 7-(2,6-Dichlorobenzoylamino)-2-methyl-3-([N-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)]carbamoylmethyl)-benzo[b]furan

mp : >260°C

25 NMR (DMSO-d₆, δ) : 2.47 (3H, s), 4.00 (2H, s), 7.21 (1H, t, J=8Hz), 7.38 (1H, d, J=8Hz), 7.40-7.60 (3H, m), 7.79 (1H, d, J=8Hz)

Example 24 (8)

7-(2,6-Dichlorobenzoylamino)-2,3-dimethyl-5-(4-methylpiperazin-1-yl)carbonylbenzo[b]furan

mp : 128-138°C

30 NMR (CDCl₃, δ) : 2.15 (3H, s), 2.34 (3H, s), 2.38 (3H, s), 2.40-2.60 (4H, m), 3.50-3.70 (2H, m), 3.70-3.90 (2H, m), 7.30-7.45 (3H, m), 7.93 (1H, s), 8.31 (1H, s)

35 Example 24 (9)

- 140 -

7-(2,6-Dichlorobenzoylamino)-2,3-dimethyl-5-(morpholin-4-yl)carbonylbenzo[b]furan

mp : 219-221°C

5 NMR (CDCl₃, δ) : 2.16 (3H, s), 2.39 (3H, s), 3.60-3.90 (8H, m), 7.30-7.45 (3H, m), 7.90 (1H, s), 8.31 (1H, s)

Example 24 (10)

10 5-(2,6-Dichlorobenzoylamino)-5-(dimethylamino)acetyl-2,3-dimethylbenzo[b]furan

mp : 115-119°C

15 NMR (DMSO-d₆, δ) : 2.11 (3H, s), 2.30 (6H, s), 2.38 (3H, s), 3.08 (2H, s), 7.42-7.62 (3H, m), 7.78 (1H, s), 7.99 (1H, s), 9.80 (1H, s)

Example 24 (11)

5-(Acetyl-2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan

mp : >250°C

20 NMR (DMSO-d₆, δ) : 1.89 (3H, s), 2.10 (3H, s), 2.38 (3H, s), 3.88 (2H, d, J=6Hz), 7.43-7.62 (3H, m), 7.75 (1H, s), 7.95 (1H, s), 8.20 (1H, t, J=6Hz), 10.03 (1H, s)

25 Example 25

A solution of 7-(2,6-dichlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan (150 mg) in 4N-hydrogenchloride in ethyl acetate was refluxed for 2 hours. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel. The obtained oil was crystallized from a mixture of diethyl ether and hexane to give 7-(2,6-dichlorobenzoylamino)-2-methyl-3-(1-methylvinyl)benzo[b]furan (72 mg).

35 mp : 147-148°C

- 141 -

NMR (CDCl₃, δ) : 2.18 (3H, s), 2.49 (3H, s), 5.10 (1H, s), 5.30 (1H, s), 7.20-7.45 (5H, m), 7.82 (1H, br s), 8.30 (1H, d, J=8Hz)

5 Example 26

A solution of 7-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-methylbenzo[b]furan (140 mg), triethylamine (61 mg) and ethyl isocyanate (35 mg) in dichloromethane was stirred at ambient temperature for 5 hours. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel. The obtained oil was crystallized from diethyl ether to give 7-(2,6-dichlorobenzoylamino)-3-(N-ethylcarbamoyloxymethyl)-2-methylbenzo[b]furan (125 mg).

15 mp : 225-226°C

NMR (CDCl₃, δ) : 1.12 (3H, t, J=8Hz), 2.49 (3H, s), 3.21 (2H, m), 4.65 (1H, m), 5.18 (2H, s), 7.25-7.45 (5H, m), 7.82 (1H, br s), 8.31 (1H, d, J=8Hz)

20

The following compound was obtained according to a similar manner to that of Preparation 39 (1).

Example 27

25 7-(2,6-Dichlorobenzoylamino)-3-(1-hydroxyiminoethyl)-2-methylbenzo[b]furan

mp : 237-238°C

NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.35 (3H, s), 2.57 (3H, s), 7.27 (1H, t, J=8Hz), 7.30-7.45 (3H, m), 7.49 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz)

30

Example 28

A mixture of 3-(1-cyclohexyl)hydroxymethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (65 mg) and triethylsilane (87 mg) in trifluoroacetic acid (3 ml) was

35

- 142 -

stirred at ambient temperature for overnight. The reaction mixture was concentrated in vacuo. To the residue was added aqueous saturated sodium bicarbonate and the separated oil was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from hexane to give 3-cyclohexylmethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (42 mg).

mp : 189-190°C

NMR (CDCl₃, δ) : 0.85-1.10 (2H, m), 1.10-1.30 (3H, m), 1.50-1.80 (6H, m), 2.37 (3H, s), 2.47 (2H, d, J=8Hz), 7.20-7.30 (2H, m), 7.30-7.45 (3H, m), 7.82 (1H, br s), 8.38 (1H, m)

Example 29

A mixture of 7-(2,6-dichlorobenzoylamino)-2-methyl-3-(4-succinimidylloxycarbonylbutyryl)oxymethyl, benzo[b]furan (112 mg), aminomethylenebis(phosphonic acid) (77 mg) and triethylamine (162 mg) in N,N-dimethylformamide (2 ml) and water (0.5 ml) was stirred at ambient temperature for 3 hours. Then, the reaction mixture was poured into cold water. The aqueous solution was washed with ethyl acetate and the pH of the solution was adjusted to 2 with 2N-hydrochloric acid. The separated solid was collected, washed with ethyl acetate and water and dried to give 4-[[7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan-3-yl]methyloxycarbonyl]butyrylaminomethylenebis(phosphonic acid) (50 mg).

mp : 190-195°C

NMR (DMSO-d₆, δ) : 1.73 (2H, quint., J=7Hz), 2.20 (2H, t, J=7Hz), 2.32 (2H, t, J=7Hz), 4.43 (1H, dt, J=9 and 20Hz), 5.22 (2H, s), 7.25 (1H, t, J=8Hz), 7.41 (1H, d, J=8Hz), 7.45-7.60 (3H, m), 7.80 (1H, d, J=8Hz)

- 143 -

Example 30

Nitric acid (d; 1.5, 0.033 ml) was added to a solution of 6-(2,6-dichlorobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran (200 mg) in acetic acid at 4°C.

5 The mixture was stirred at ambient temperature for 5 hours and poured into cold water. The separated solid was collected and washed with isopropyl alcohol to give 6-(2,6-dichlorobenzoylamino)-7-nitro-1,2,3,4-tetrahydrodibenzofuran (17 mg).

10 mp : 246-248°C

NMR (CDCl₃, δ) : 1.81-2.06 (4H, m), 2.61-2.72 (2H, m), 2.80-2.90 (2H, m), 7.29-7.46 (4H, m), 8.06 (1H, d, J=8Hz), 9.21 (1H, br s)

15 Example 31

A solution of 5-carboxy-7-(2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan (152 mg) and triethylamine (61 mg) in dichloromethane (3 ml) was stirred at -20°C and to the solution was added isobutyl chloroformate (66 mg).

20 The mixture was stirred at -20°C for 3 hours and added to cold (-20°C) solution of 10% ammonia in methanol (3 ml). The reaction mixture was stirred at ambient temperature for 10 minutes and partitioned between dichloromethane and water. The organic layer was washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from ethyl acetate to give 5-carbamoyl-7-(2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan (70 mg).

25 mp : >250°C

30 NMR (CDCl₃:CD₃OD = 1:1, δ) : 2.19 (3H, s), 2.40 (3H, s), 7.30-7.50 (3H, m), 7.90 (1H, s), 8.45 (1H, s)

35 Example 32

- 144 -

A mixture of 5-amino-7-(2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan hydrochloride (155 mg), triethylamine (61 mg) and trichloroacetyl isocyanate (115 mg) was stirred at ambient temperature for 1 hour. Then, the mixture was concentrated in vacuo and to the residue was added methanol (3 ml) and aqueous 1N-sodium hydroxide (2 ml). The mixture was stirred at 60°C for 15 minutes and the methanol was evaporated in vacuo. The separated solid was collected, washed with water and dried to give 7-(2,6-dichlorobenzoylamino)-2,3-dimethyl-5-ureidobenzo[b]furan (130 mg).

mp : >250°C

NMR (DMSO-d₆, δ) : 2.10 (3H, s), 2.37 (3H, s), 5.75 (2H, s), 7.40-7.63 (4H, m), 7.67 (1H, s), 8.63 (1H, s)

Example 33

A mixture of 3-chloromethyl-7-(2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan (20 mg) and potassium carbonate (7.5 mg) in methanol was refluxed for 1 hour. The mixture was cooled and poured into water. The separated oil was extracted with ethyl acetate and the extract was washed with water, dried over sodium sulfate and evaporated in vacuo. The residue was purified by preparative TLC to give 7-(2,6-dichlorobenzoylamino)-2,3-dihydro-2-methoxy-2-methyl-3-methylenebenzo[b]furan (5 mg).

mp : 208-210°C

NMR (CDCl₃, δ) : 1.64 (3H, s), 3.16 (3H, s), 5.20 (1H, s), 5.71 (1H, s), 7.00 (1H, t, J=7.5Hz), 7.22 (1H, d, J=7.5Hz), 7.30-7.50 (3H, m), 7.61 (1H, br s), 8.38 (1H, d, J=7.5Hz)

Example 34

A mixture of 6-(2,6-dichlorobenzoylamino)-1-hydroxy-

- 145 -

1,2,3,4-tetrahydrodibenzofuran (500 mg), methanesulfonyl chloride (880 mg) and triethylamine (1.19 g) in dichloromethane was refluxed for 4 hours. The mixture was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of 2-propanol and water to give 6-(2,6-dichlorobenzoylamino)-3,4-dihydrodibenzofuran (173 mg).

mp : 165-167°C

NMR (CDCl₃, δ) : 2.58-2.68 (2H, m), 2.95 (2H, t, J=9Hz), 5.77 (1H, m), 6.50 (1H, d, J=9Hz), 7.23-7.42 (5H, m), 7.82 (1H, br s), 8.29 (1H, d, J=8Hz)

Example 35

A mixture of 6-(2,6-dichlorobenzoylamino)-3,4-dihydrodibenzofuran (100 mg), 4-methylmorpholine N-oxide (39 mg) and osmium tetroxide (10% solution in tert-butanol, 1 drop) in a mixture of acetone (2 ml) and water (0.5 ml) was stirred at ambient temperature for 6 hours. The mixture was partitioned between 1% aqueous sodium bisulfite and ethyl acetate. The organic layer was separated, washed with aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 7-(2,6-dichlorobenzoylamino)-1,2-dihydroxy-1,2,3,4-tetrahydrodibenzofuran (74 mg).

mp : 206-209°C

NMR (DMSO-d₆, δ) : 1.80 (1H, m), 2.07 (1H, m), 2.69-2.84 (2H, m), 3.83 (1H, m), 4.63 (1H, d, J=6Hz), 4.71 (1H, m), 5.94 (1H, d, J=6Hz), 7.22 (1H, t, J=8Hz), 7.40 (1H, d, J=8Hz), 7.49 (1H, t,

- 146 -

J=8Hz), 7.57 (2H, d, J=8Hz), 7.80 (1H, d, J=8Hz)

Example 36

A solution of hydrogen peroxide in trifluoroacetic acid (1M, 0.32 ml) was added to a solution of 6-(2,6-dichlorobenzoylamino)-3,4-dihydro-1H-thiopyrano-[4,3-b]benzofuran (120 mg) in trifluoroacetic acid (2.5 ml) at 4°C. The mixture was stirred at ambient temperature for 30 minutes and to the mixture was added water. The separated solid was collected and dried. The obtained solid was suspended in hot ethanol and to the mixture was added water. The mixture was cooled and the separated solid was collected to give 6-(2,6-dichlorobenzoylamino)-3,4-dihydro-1H-thiopyrano[4,3-b]-benzofuran 2-oxide (70 mg).

mp : >250°C

NMR (DMSO-d₆, δ) : 3.10-3.20 (2H, m), 3.30-3.50 (2H, m), 4.03-4.12 (2H, m), 7.28 (1H, t, J=8Hz), 7.40 (1H, d, J=8Hz), 7.46-7.61 (3H, m), 8.85 (1H, d, J=8Hz)

The following compounds [Examples 37 (1) to (3)] were obtained according to a similar manner to that of Preparation 42 (1).

Example 37 (1)

6-(3-Amino-2,6-dichlorobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran

mp : 197-200°C

NMR (CDCl₃, δ) : 1.80-2.00 (4H, m), 2.60-2.78 (4H, m), 4.26 (2H, br s), 6.80 (1H, d, J=8Hz), 7.18 (1H, d, J=8Hz), 7.20-7.30 (2H, m), 7.88 (1H, br s), 8.32 (1H, m)

- 147 -

Example 37 (2)

3-Acetyl-7-(3-amino-2,6-dichlorobenzoylamino)-2-methylbenzo[b]furan

mp : >250°C

5 NMR (DMSO-d₆, δ) : 2.61 (3H, s), 2.79 (3H, s), 5.72 (2H, s), 6.87 (1H, d, J=8Hz), 7.19 (1H, d, J=8Hz), 7.33 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz)

10 Example 37 (3)

7-(3-Amino-2,6-dichlorobenzoylamino)-2,3-dimethylbenzo[b]furan

mp : 245-246.5°C

15 NMR (DMSO-d₆, δ) : 2.15 (3H, s), 2.39 (3H, s), 5.68 (2H, br s), 6.83 (1H, d, J=8Hz), 7.19 (2H, m), 7.30 (1H, d, J=8Hz), 7.72 (1H, d, J=8Hz)

Example 38 (1)

20 To a mixture of 6-(3-amino-2,6-dichlorobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran (100 mg) and triethylamine (54 mg) in chloroform (3 ml) was added chloroacetyl chloride (36 mg) under ice cooling. The mixture was stirred at ambient temperature for 2 hours, and then dimethyl amine hydrochloride (65 mg) was added to the mixture and additionally the mixture was stirred for 12 hours. The mixture was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluting with (ethyl acetate : n-hexane = 1:1) and the obtained oil was crystallized from ethanol to give 6-[2,6-dichloro-3-(2-dimethylaminoacetylamino)benzoylamino]-1,2,3,4-tetrahydrodibenzofuran (62 mg).

mp : 207°C

35 NMR (CDCl₃, δ) : 1.79-2.00 (4H, m), 2.42 (6H, s), 2.59-2.77 (4H, m), 3.15 (2H, s), 7.24 (2H, m),

- 148 -

7.40 (1H, d, J=8Hz), 7.89 (1H, br s), 8.29 (1H, dd, J=1 and 8Hz), 8.51 (1H, d, J=8Hz), 9.99 (1H, br s)

5 The following compounds [Examples 38 (2) to (6)] were obtained according to a similar manner to that of Example 38 (1).

Example 38 (2)

10 7-(2,6-Dichloro-3-dimethylaminoacetylaminobenzoyl-amino)-2,3-dimethylbenzo[b]furan

mp : 211.5-213°C

NMR (CDCl₃, δ) : 2.15 (3H, s), 2.37 (3H, s), 2.41 (6H, s), 3.13 (2H, s), 7.22 (2H, m), 7.40 (1H, d, J=8Hz), 7.83 (1H, br s), 8.28 (1H, d, J=8Hz), 8.51 (1H, d, J=8Hz)

Example 38 (3)

20 6-[2,6-Dichloro-3-(morpholin-4-yl)-acetylaminobenzoylamino]-1,2,3,4-tetrahydrodibenzofuran

mp : 252-254°C

NMR (CDCl₃, δ) : 1.79-2.02 (4H, m), 2.60-2.78 (8H, m), 3.23 (2H, s), 3.72-3.82 (4H, m), 7.25 (2H, d, J=6Hz), 7.40 (1H, d, J=8Hz), 7.89 (1H, br s), 8.28 (1H, dd, J=6 and 6Hz), 8.56 (1H, d, J=8Hz), 10.07 (1H, br s)

Example 38 (4)

30 3-Acetyl-7-(2,6-dichloro-3-dimethylaminoacetylaminobenzoylamino)-2-methylbenzo[b]furan

mp : 235-236°C

NMR (CDCl₃, δ) : 2.42 (6H, s), 2.66 (3H, s), 2.79 (3H, s), 3.15 (2H, s), 7.35-7.40 (2H, m), 7.72 (1H, d, J=8Hz), 7.90 (1H, s), 8.32 (1H, d, J=8Hz), 8.51 (1H, d, J=8Hz)

- 149 -

Example 38 (5)

6-[2,6-Dichloro-3-[bis(2-methoxyethyl)aminoacetyl-
amino]benzoylamino]-1,2,3,4-tetrahydrodibenzofuran

mp : 168.5-170.0°C

5 NMR (CDCl₃, δ) : 1.80-1.99 (4H, m), 2.60-2.68 (2H,
m), 2.68-2.77 (2H, m), 2.88 (4H, t, J=5Hz), 3.28
(6H, s), 3.44 (2H, s), 3.50 (4H, t, J=5Hz),
7.22-7.28 (2H, m), 7.38 (1H, d, J=8Hz), 7.67
(1H, br s), 8.30 (1H, dd, J=1.5 and 7Hz), 8.58
10 (1H, d, J=8Hz)

Example 38 (6)

6-(2,6-Dichloro-3-ureidobenzoylamino)-1,2,3,4-
tetrahydrodibenzofuran

15 mp : 242-244°C

NMR (DMSO-d₆, δ) : 1.71-1.98 (4H, m), 2.53-2.79 (4H,
m), 6.51 (2H, br s), 7.20 (1H, t, J=8Hz), 7.30
(1H, d, J=8Hz), 7.43 (1H, d, J=8Hz), 7.82 (1H,
d, J=8Hz), 8.20-8.30 (2H, m)

20

Example 39 (1)

A mixture of 6-(3-amino-2,6-dichlorobenzoylamino)-
1,2,3,4-tetrahydrodibenzofuran (100 mg), methanesulfonyl
chloride (120 mg) and triethylamine (162 mg) in
25 dichloromethane (3 ml) was stirred at ambient temperature
for 2 hours. The reaction mixture was diluted with
dichloromethane and washed with 1N-hydrochloric acid,
aqueous saturated sodium bicarbonate and brine. The
solution was dried over sodium sulfate and concentrated in
30 vacuo. The residual oil was crystallized from ethanol to
give 6-[2,6-dichloro-3-bis(methanesulfonyl)aminobenzoyl-
amino]-1,2,3,4-tetrahydrodibenzofuran (87 mg).

mp : 237-238.5°C

35 NMR (CDCl₃, δ) : 1.78-2.01 (4H, m), 2.57-2.80 (4H,
m), 3.50 (6H, s), 7.23 (2H, d, J=6Hz), 7.43 (1H,

- 150 -

d, J=8Hz), 7.50 (1H, d, J=8Hz), 7.98 (1H, br s),
8.25 (1H, t, J=6Hz)

5 The following compounds [Examples 39 (2) to (5)] were
obtained according to a similar manner to that of Example
39 (1).

Example 39 (2)

6-(3-Acetoxyacetyl-amino-2,6-dichlorobenzoylamino)-
10 1,2,3,4-tetrahydrodibenzofuran
mp : 225-227°C
NMR (CDCl₃, δ) : 1.78-2.00 (4H, m), 2.24 (3H, s),
2.58-2.77 (4H, m), 4.75 (2H, s), 7.20-7.29 (2H,
m), 7.41 (1H, d, J=8Hz), 7.88 (1H, br s), 8.27
15 (1H, dd, J=6 and 6Hz), 8.46-8.55 (2H, m)

Example 39 (3)

6-(2,6-Dichloro-3-methoxyacetylaminobenzoylamino)-
1,2,3,4-tetrahydrodibenzofuran
20 mp : 217°C
NMR (CDCl₃, δ) : 1.79-2.01 (4H, m), 2.60-2.78 (4H,
m), 3.55 (3H, s), 4.09 (2H, s), 7.24 (2H, d,
J=6Hz), 7.40 (1H, d, J=8Hz), 7.90 (1H, br s),
8.29 (1H, m), 8.52 (1H, d, J=8Hz), 8.98 (1H, br
25 s)

Example 39 (4)

7-(2,6-Dichlorobenzoylamino)-2,3-dimethyl-5-
(morpholin-4-yl)carbonylaminobenzo[b]furan
30 mp : >250°C
NMR (DMSO-d₆, δ) : 2.10 (3H, s), 2.37 (3H, s),
3.38-3.50 (4H, m), 3.57-3.60 (4H, m), 7.40-7.60
(4H, m), 7.87 (1H, s), 8.61 (1H, s)

35 Example 39 (5)

- 151 -

7-(2,6-Dichlorobenzoylamino)-2-methyl-3-(morpholin-4-yl)carbonylaminomethylbenzo[b]furan

mp : >250°C

5 NMR (CDCl₃:CD₃OD = 9:1, δ) : 2.48 (3H, s), 3.33 (4H, t, J=5Hz), 3.68 (4H, t, J=5Hz), 4.45 (2H, d, J=6Hz), 5.25 (1H, t, J=6Hz), 7.25 (1H, t, J=7Hz), 7.30-7.45 (4H, m), 8.17 (1H, d, J=7Hz)

Example 40 (1)

10 A mixture of 6-(3-amino-2,6-dichlorobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran (100 mg), aqueous 37% formaldehyde, sodium cyanoborohydride (70 mg) and acetic acid (5 drops) in acetonitrile (2 ml) was stirred at ambient temperature for 3 hours. The reaction mixture was
15 partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by preparative TLC on silica gel and the obtained oil was
20 crystallized from diisopropyl ether to give 6-(2,6-dichloro-3-methylaminobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran (21 mg).

mp : 160-162°C

25 NMR (CDCl₃, δ) : 1.78-2.00 (4H, m), 2.58-2.78 (4H, m), 2.93 (3H, d, J=6Hz), 4.52 (1H, m), 6.64 (1H, d, J=8Hz), 7.18-7.30 (3H, m), 7.83 (1H, br s), 8.31 (1H, dd, J=1 and 8Hz)

30 The following compound was obtained according to a similar manner to that of Example 40 (1).

Example 40 (2)

7-(2-Chloro-6-dimethylaminobenzoylamino)-2,3-dimethylbenzo[b]furan

35 mp : 118-119°C

- 152 -

NMR (CDCl₃, δ) : 2.15 (3H, s), 2.37 (3H, s), 2.87 (6H, s), 6.94 (1H, d, J=8Hz), 7.04 (1H, d, J=8Hz), 7.17-7.30 (3H, m), 8.26-8.31 (2H, m)

5 Example 41

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1M solution, 0.58 ml) was added to a solution of 7-(2,6-dichloro-3-triisopropylsilyloxybenzoylamino)-2,3-dimethylbenzo[b]furan (221 mg) in tetrahydrofuran (2 ml) at 4°C. The solution was stirred at 4°C for 1 hour and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 7-(2,6-dichloro-3-hydroxybenzoylamino)-2,3-dimethylbenzo[b]furan (152 mg).

mp : 191.5-193.5°C

NMR (CDCl₃, δ) : 2.14 (3H, s), 2.36 (3H, s), 5.78 (1H, br s), 7.05 (1H, d, J=8Hz), 7.20-7.31 (3H, m), 7.80 (1H, br s), 8.26 (1H, d, J=8Hz)

Example 42

A solution of 7-[2,6-dichloro-3-(2-methoxyethyl)oxymethoxymethylbenzoylamino]-2,3-dimethylbenzo[b]furan (305 mg) in 10% methanolic hydrogen chloride (4.5 ml) was refluxed for 1 hour. The reaction mixture was cooled and the separated solid was collected to give 7-(2,6-dichloro-3-hydroxymethylbenzoylamino)-2,3-dimethylbenzo[b]furan (217 mg).

mp : 258-261°C

NMR (DMSO-d₆, δ) : 2.15 (3H, s), 2.39 (3H, s), 4.60 (2H, d, J=5Hz), 5.61 (1H, t, J=5Hz), 7.21 (1H, t, J=8Hz), 7.31 (1H, d, J=8Hz), 7.57 (1H, d, J=8Hz), 7.62 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz)

- 153 -

Example 43

Aqueous saturated ammonium chloride (1 ml) was added dropwise to a suspension of 6-(2,6-dichloro-3-nitrobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran (150 mg) and zinc (120 mg) in a mixture of tetrahydrofuran (1.5 ml) and ethanol (1 ml). The mixture was diluted with chloroform and the insoluble matter was filtered off. The organic layer of the filtrate was separated, washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was crystallized from ethyl acetate to give 6-(2,6-dichloro-3-hydroxyaminobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran (40 mg).

mp : 175°C (dec.)

NMR (DMSO-d₆, δ) : 1.73-1.96 (4H, m), 2.54-2.68 (2H, m), 2.68-2.78 (2H, m), 7.15-7.25 (2H, m), 7.30 (1H, d, J=8Hz), 7.40 (1H, d, J=8Hz), 7.78 (1H, d, J=8Hz), 8.56 (1H, br s), 8.78 (1H, m)

The following compound was obtained according to a similar manner to that of Preparation 2 (1).

Example 44

7-(2,6-Dichloro-3-ethoxycarbonylmethoxybenzoylamino)-2,3-dimethylbenzo[b]furan

mp : 131-133°C

NMR (CDCl₃, δ) : 1.32 (3H, t, J=7Hz), 2.16 (3H, s), 2.38 (3H, s), 4.29 (2H, q, J=7Hz), 4.73 (2H, s), 6.88 (1H, d, J=8Hz), 7.20-7.27 (2H, m), 7.31 (1H, d, J=8Hz), 7.80 (1H, br s), 8.28 (1H, d, J=8Hz)

Example 45 (1)

A mixture of 6-(3-acetoxyacetyl-amino-2,6-dichlorobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran (67 mg) and aqueous 1N-sodium hydroxide (0.5 ml) in a mixture

- 154 -

of dichloromethane (1 ml) and methanol (1 ml) was stirred at ambient temperature for 1 hour. The mixture was partitioned between a mixture of dichloromethane and ethanol (8:2) and water. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was crystallized from ethanol to give 6-(2,6-dichloro-3-hydroxyacetyl-amino-benzoylamino)-1,2,3,4-tetrahydrodibenzofuran (30 mg).

mp : 245-249°C

10 NMR (CDCl₃:CD₃OD = 9:1, δ) : 1.80-2.00 (4H, m), 2.58-2.80 (4H, m), 4.20 (2H, s), 7.24 (2H, d, J=5Hz), 7.41 (1H, d, J=8Hz), 8.20 (1H, t, J=5Hz), 8.47 (1H, d, J=8Hz)

15 The following compound was obtained according to a similar manner to that of Example 45 (1).

Example 45 (2)

20 6-(2,6-Dichloro-3-methanesulfonylamino-benzoylamino)-1,2,3,4-tetrahydrodibenzofuran.

mp : 202-204°C

25 NMR (CDCl₃, δ) : 1.79-2.01 (4H, m), 2.59-2.78 (4H, m), 3.08 (3H, s), 6.89 (1H, br s), 7.25 (2H, d, J=5Hz), 7.43 (1H, d, J=8Hz), 7.73 (1H, d, J=8Hz), 7.87 (1H, br s), 8.26 (1H, t, J=5Hz)

The following compound was obtained according to a similar manner to that of Preparation 43 (1).

30 Example 46

7-(2-Amino-6-methylbenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylbenzo[b]furan

mp : 127-128°C

35 NMR (CDCl₃, δ) : 1.71 (6H, s), 1.80 (1H, s), 2.45 (3H, s), 2.56 (3H, s), 4.28 (2H, br s), 6.60

- 155 -

(1H, d, J=8Hz), 6.66 (1H, d, J=8Hz), 7.12 (1H, t, J=8Hz), 7.20 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 7.91 (1H, br s), 8.23 (1H, d, J=8Hz)

5 The following compound was obtained according to a similar manner to that of Preparation 18 (1).

Example 47

9-Acetyl-6-(2,6-dichlorobenzoylamino)-1,2,3,4-tetrahydrodibenzofuran

mp : 212-214°C

NMR (CDCl₃, δ) : 1.75-1.95 (4H, m), 2.67 (3H, s),
2.73 (2H, m), 2.90 (2H, m), 7.30-7.45 (3H, m),
7.72 (1H, d, J=7Hz), 8.02 (1H, br s), 8.38 (1H, d, J=7Hz)

The following compound was obtained according to a similar manner to that of Preparation 14.

20 Example 48

7-(2,6-Dichlorobenzoyl)-2,3,5-trimethylbenzo[b]furan

mp : 143-146°C

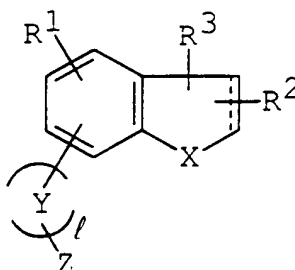
NMR (CDCl₃, δ) : 2.13 (3H, s), 2.29 (3H, s),
2.45 (3H, s), 7.30-7.50 (5H, m)

30

- 156 -

C L A I M S

1. A compound of the formula :



wherein

R^1 is hydrogen, lower alkyl, an acyl group, amino, acylamino, nitro, halogen or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^2 is hydrogen, lower alkyl, an acyl group, lower alkoxy, acyl(lower)alkyl, aryl, cyano, mono-(or di- or tri-)halo(lower)alkyl, lower alkylthio or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^3 is hydrogen, lower alkyl, lower alkenyl, cyclo(lower)alkyl(lower)alkyl, halogen, an acyl group, acyl(lower)alkyl, acylamino, acylamino(lower)alkyl, acyl(lower)alkenyl, acyloxy(lower)alkyl, acyl(lower)alkylthio(lower)alkyl, amino(lower)alkyl, mono-(or di-)lower alkylamino, lower alkylthio(lower)alkyl, hydroxyimino(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkylthio(lower)alkyl, cyano(lower)alkyl, mono-(or di-)lower alkoxy(lower)alkyl which may have one or more suitable substituent(s), lower alkyl substituted with aryl which may have one or more suitable substituent(s), mono-(or di-)lower-alkylamino(lower)alkyl, lower alkyl substituted with heterocyclic group which may have one or more suitable

- 157 -

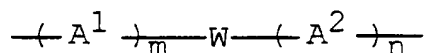
substituent(s), heterocyclic group which may have one or more suitable substituent(s), heterocyclithio, heterocyclithio(lower)alkyl, heterocyclicoxy, heterocyclicoxy(lower)alkyl, heterocycliaminoimino-(lower)alkyl, aryl, amino or nitro,

in which R^2 and R^3 may be linked together to form

(1) lower alkylene which may have one or more suitable substituent(s),

(2) lower alkenylene which may have one or more suitable substituent(s), or

(3) a group of the formula :



[wherein A^1 and A^2 are each lower alkylene which may have one or more suitable substituent(s) or lower alkenylene which may have one or more suitable substituent(s),

W is $-S-$, $-\overset{\overset{O}{\parallel}}{S}-$, or $-\overset{\overset{R^5}{|}}{N}-$ (wherein R^5 is hydrogen, lower alkyl or an acyl group)

and

m and n are each an integer of 0 or 1,],

X is O or S,

Y is vinylene, or a group of the formula :

$-\text{NHCO}-$, $-\text{NHSO}_2-$, $-\text{OCO}-$, $-\text{OCH}_2-$, $-\text{NHCOCO}-$,
 $-\text{NHCOCH}=\text{CH}-$, $-\text{NHCOCH}_2-$, $-\text{NHCONH}-$ or $-\text{N}-\overset{\overset{R^6}{|}}{\text{CO}}-$
 (wherein R^6 is lower alkyl),

Z is heterocyclic group which may have one or more suitable substituent(s), or aryl which may have one or more suitable substituent(s),

l is an integer of 0 or 1, and

---- is a single bond or a double bond,

and a pharmaceutically acceptable salt thereof.

- 158 -

2. A compound of claim 1, wherein

R^1 is hydrogen, lower alkyl, an acyl group, amino, acylamino, nitro, halogen, or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^2 is lower alkyl or acyl(lower)alkyl,

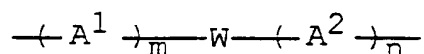
R^3 is hydrogen, lower alkyl, lower alkenyl, cyclo(lower)alkyl(lower)alkyl, halogen, an acyl group, acyl(lower)alkyl, acylamino, acylamino(lower)alkyl, acyl(lower)alkenyl, acyloxy(lower)alkyl, acyl(lower)alkylthio(lower)alkyl, amino(lower)alkyl, mono-(or di-)lower alkylamino, lower alkylthio(lower)alkyl, mono-(or di-)lower alkoxy(lower)alkyl which may have one or more suitable substituent(s), hydroxyimino(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkylthio(lower)alkyl, lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), heterocyclic group which may have one or more suitable substituent(s), or heterocyclicthio(lower)alkyl,

in which R^2 and R^3 may be linked together to form

(1) lower alkylene which may have one or more suitable substituent(s),

(2) lower alkenylene which may have one or more suitable substituent(s), or

(3) a group of the formula :



[wherein A^1 and A^2 are each lower alkylene which may have one or more suitable substituent(s), and

W is -S-, $\overset{\text{O}}{\parallel}\text{-S-}$ or $\overset{\text{R}^5}{\text{N-}}$ (wherein R^5 is hydrogen, or an acyl group),

and

- 159 -

m and n are each an integer of 0 or 1.]

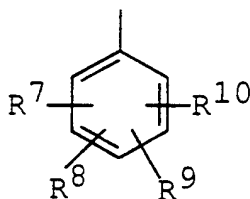
X is O,

Y is vinylene, or a group of the formula :

-NHCO-, -NHSO₂-, -OCO- or -OCH₂-,

Z is heterocyclic group which may have one or more suitable substituent(s), naphthyl which may have one or more suitable substituent(s),

or a group of the formula :



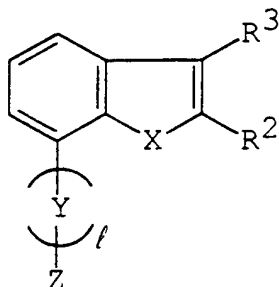
[wherein

R⁷, R⁸, R⁹ and R¹⁰ are each hydrogen, halogen, lower alkyl, nitro, lower alkoxy, an acyl group, cyclo(lower)alkyl, mono-(or di- or tri-)halo(lower)alkyl, acylamino, aryl, amino, hydroxyamino, mono-(or di-)lower alkylamino, aryloxy, aryl(lower)alkoxy, hydroxy, hydroxy(lower)alkyl which may have one or more suitable substituent(s), heterocyclic group which may have one or more suitable substituent(s), mono-(or di-)lower-alkylamino(lower)alkyl or acyl(lower)alkoxy,], and

l is an integer of 0 or 1.

3. A compound of claim 2, which is shown by the following formula :

- 160 -



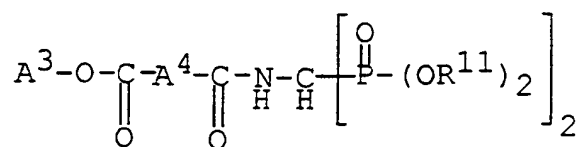
wherein

R^2 is lower alkyl, carboxy(lower)alkyl or protected carboxy(lower)alkyl,

R^3 is hydrogen, lower alkyl, lower alkenyl, cyclo(lower)alkyl(lower)alkyl, cyclo(lower)-alkylcarbonyloxy(lower)alkyl, halogen, lower alkanoyl, heterocyclic carbonyl(lower)alkyl, lower alkanoylamino, lower alkoxy carbonylamino(lower)alkyl, lower alkanoylamino(lower)alkyl, heterocyclic carbonylamino(lower)alkyl, carboxy(lower)alkenyl, protected carboxy(lower)alkenyl, lower alkanoyloxy(lower)alkyl, aroyloxy(lower)alkyl, protected carboxy(lower)alkyl, protected carboxy(lower)alkylthio(lower)alkyl, amino(lower)alkyl, di-lower alkylamino, di-lower alkylaminocarbonyl(lower)-alkyl, lower alkylaminocarbonyloxy(lower)alkyl, cyclo(lower)alkylaminocarbonyl(lower)alkyl, carboxy(lower)alkyl, protected carboxy(lower)alkyl, lower alkylthio(lower)alkyl, di-lower alkoxyphosphoryl(lower)alkyl, di-lower alkoxyphosphoryloxy(lower)alkyl, hydroxyimino(lower)alkyl, hydroxy(lower)alkyl which may have 1 to 3 suitable substituent(s), hydroxy(lower)alkylthio(lower)alkyl, di-lower alkylaminocarbonyl(lower)alkyl, carboxy(lower)alkanoxy(lower)alkyl, lower alkoxy(lower)alkyl, hydroxy(lower)-

- 161 -

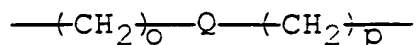
alkylaminocarbonyl(lower)alkyl, lower
 alkoxy(lower)alkylaminocarbonyl(lower)alkyl,
 aminocarbonyl(lower)alkyl substituted with heterocyclic
 group which may have 1 to 3 suitable substituent(s),
 heterocyclic(lower)alkyl, heterocyclic(lower)-
 alkylaminocarbonyl(lower)alkyl, heterocyclic group which
 may have 1 to 3 suitable substituent(s)
 heterocyclicthio(lower)alkyl,
 or a group of the formula :



[wherein A³ is lower alkylene which may have 1 to 3 suitable
 substituent(s),

R¹¹ is hydrogen or lower alkyl, and

A⁴ is lower alkylene or a group of the formula :



(wherein Q is phenylene which may have 1 to 3

suitable substituent(s) or

cyclo(lower)alkylene which may have 1
 to 3 suitable substituent(s), and

o and p are each of integer of 0 or 1),],

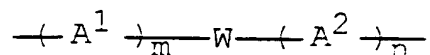
in which R² and R³ may be linked together to form

(1) lower alkylene which may have 1 to 3 suitable
 substituent(s),

(2) lower alkenylene which may have 1 to 3 suitable
 substituent(s), or

(3) a group of the formula :

- 162 -



[wherein A¹ and A² are each lower alkylene which may have 1 to 3 suitable substituent(s),

W is -S-, $\overset{\text{O}}{\parallel}\text{-S-}$ or $\overset{\text{R}^5}{\text{N-}}$ (wherein R⁵ is hydrogen, or an acyl group)

and

m and n are each an integer of 0 or 1,],

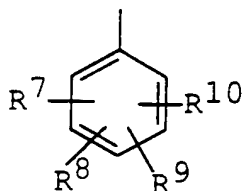
X is O,

Y is vinylene, or a group of the formula :

-NHCO-, -NHSO₂-, -OCO- or -OCH₂-,

Z is heterocyclic group which may have 1 to 3 suitable substituent(s), naphthyl which may have 1 to 3 suitable substituent(s),

or a group of the formula :



[wherein

R⁷, R⁸, R⁹ and R¹⁰ are each hydrogen, halogen, lower alkyl, nitro, lower alkoxy, carbamoyl, protected carboxy, carboxy, aroyl, cyclo(lower)alkyl, tri-halo(lower)alkyl, lower alkanoylamino, ureido, aryl, amino, mono- or di-lower alkylamino, hydroxyamino, aryloxy, aryl(lower)alkoxy, hydroxy, hydroxy(lower)alkyl which may have 1 to 3 suitable substituent(s), heterocyclic group which may have 1 to 3 suitable substituent(s), lower alkanoyloxy(lower)alkanoylamino, heterocyclic-

- 163 -

(lower)alkanoylamino, lower alkoxy(lower)alkanoylamino, hydroxy(lower)alkanoylamino, di-(lower)alkylamino-(lower)alkyl, protected carboxy(lower)alkoxy, di-(lower)alkylamino(lower)alkanoylamino, lower alkylsulfonylamino, or bis{lower alkoxy(lower)alkyl}amino(lower)alkanoylamino,], and l is an integer of 0 or 1.

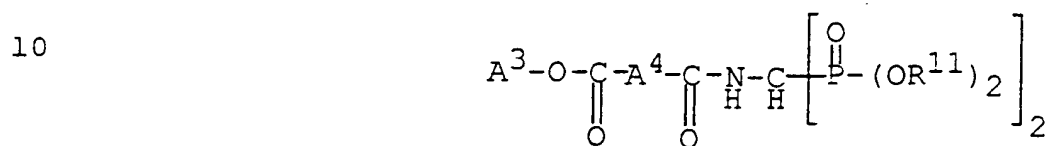
4. A compound of claim 3, wherein

R^2 is lower alkyl, carboxy(lower)alkyl or protected carboxy(lower)alkyl,

R^3 is hydrogen, lower alkyl, lower alkenyl, cyclo(lower)alkyl(lower)alkyl, cyclo(lower)alkylcarbonyloxy(lower)alkyl, halogen, lower alkanoyl, morpholinocarbonyl(lower)alkyl, lower alkanoylamino, lower alkoxycarbonylamino(lower)alkyl, lower alkanoylamino(lower)alkyl, morpholinocarbonylamino(lower)alkyl, carboxy(lower)alkenyl, protected carboxy(lower)alkenyl, lower alkanoyloxy(lower)alkyl, benzoyloxy(lower)alkyl, protected carboxy(lower)alkylthio(lower)alkyl, amino(lower)alkyl, di-lower alkylamino, di-lower alkylaminocarbonyl(lower)-alkyl, lower alkylaminocarbonyloxy(lower)alkyl, cyclo(lower)alkylaminocarbonyl(lower)alkyl, carboxy(lower)alkyl, protected carboxy(lower)alkyl, lower alkylthio(lower)alkyl, di-lower alkoxyphosphoryl-(lower)alkyl, di-lower alkoxyphosphoryloxy(lower)alkyl, hydroxyimino(lower)alkyl, hydroxy(lower)alkyl which may have 1 to 3 substituent(s) selected from the group consisting of protected carboxy, tri-halo(lower)alkyl, cyclo(lower)alkyl and phenyl, hydroxy(lower)alkylthio(lower)alkyl, di-lower alkylaminocarbonyl(lower)alkyl, carboxy(lower)alkanoyloxy(lower)alkyl, lower alkoxy-(lower)alkyl, hydroxy(lower)alkylaminocarbonyl(lower)-

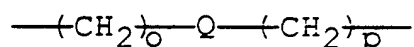
- 164 -

alkyl, lower alkoxy(lower)alkylaminocarbonyl(lower)-
 alkyl, aminocarbonyl(lower)alkyl substituted with
 thiadiazolyl having tri-halo(lower)alkyl, imidazolyl-
 (lower)alkyl, pyridyl(lower)alkylaminocarbonyl(lower)-
 5 alkyl, thiazolyl having lower alkanoylamino,
 imidazolylthio(lower)alkyl,
 or a group of the formula :



15 [wherein A³ is lower alkylene which may have 1 to 3
 substituent(s) selected from the group
 consisting of protected carboxy, tri-
 halo(lower)alkyl, cyclo(lower)alkyl and
 phenyl,

20 R¹¹ is hydrogen or lower alkyl, and
 A⁴ is lower alkylene or a group of the formula :



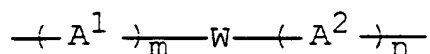
25 (wherein Q is phenylene which may have 1 to 3
 substituent(s) selected from the
 group consisting of lower alkyl and
 lower alkoxy, or cyclo(lower)alkyl
 which may have 1 to 3 substituent(s)
 30 selected from the group consisting
 of lower alkyl and lower alkoxy, and
 o and p are each an integer of 0 or 1),
 in which R² and R³ may be linked together to form
 (1) lower alkylene which may have 1 to 3 substituent(s),
 35 selected from the group consisting of lower alkyl,

- 165 -

hydroxy and oxo,

(2) lower alkenylene, or

(3) a group of the formula :



[wherein A^1 and A^2 are each lower alkylene which may have 1 to 3 substituent(s) selected from the group consisting of hydroxy and oxo,

W is -S-, $\overset{\text{O}}{\parallel}\text{-S-}$ or $\overset{\text{R}^5}{\text{N-}}$ (wherein R^5 is hydrogen or an acyl group),

and

m and n are each an integer of 0 or 1],

X is O,

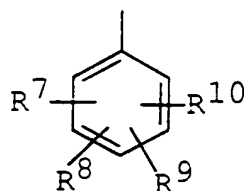
Y is vinylene, or a group of the formula :

-NHCO-, -NHSO₂-, -OCO- or -OCH₂-

Z is pyridyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, oxo, hydroxy, lower alkoxy, nitro and halogen, benzothienyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, oxo, hydroxy, lower alkoxy, nitro and halogen, indolyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, oxo, hydroxy, lower alkoxy, nitro and halogen, oxazolyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, oxo, hydroxy, lower alkoxy, nitro and halogen, pyranyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, oxo, hydroxy, lower alkoxy, nitro and halogen, pyrrolyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, oxo, hydroxy, lower alkoxy, nitro and

- 166 -

halogen, phthalimido which may have 1 to 3
 substituent(s) selected from the group consisting of
 lower alkyl, oxo, hydroxy, lower alkoxy, nitro and
 halogen, phthalimidine which may have 1 to 3
 5 substituent(s) selected from the group consisting of
 lower alkyl, oxo, hydroxy, lower alkoxy, nitro and
 halogen, naphthyl which may have 1 to 3 substituent(s)
 selected from the group consisting of lower alkyl, oxo,
 hydroxy, lower alkoxy, nitro and halogen,
 10 or a group of the formula :

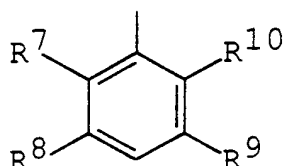


[wherein

20 R^7 , R^8 , R^9 and R^{10} are each hydrogen, halogen, lower alkyl,
 nitro, lower alkoxy, carbamoyl, protected carboxy,
 carboxy, benzoyl, cyclo(lower)alkyl, tri-
 halo(lower)alkyl, lower alkanoylamino, ureido, phenyl,
 amino, mono- or di-lower alkylamino, hydroxyamino,
 25 phenoxy, phenyl(lower)alkoxy, hydroxy,
 hydroxy(lower)alkyl, pyrrolyl which may have 1 to 3 lower
 alkyl, lower alkanoyloxy(lower)alkanoylamino, morpholino
 (lower)alkanoylamino, lower alkoxy(lower)alkanoylamino,
 hydroxy(lower)alkanoylamino, di-(lower)alkylamino-
 30 (lower)alkyl, protected carboxy(lower)alkoxy,
 di-(lower)alkylamino(lower)alkanoylamino, lower
 alkylsulfonylamino, or bis(lower
 alkoxy(lower)alkyl)amino(lower, alkanoylamino,], and
 ℓ is an integer of 0 or 1.

- 167 -

5. A compound of claim 3, wherein
Z is a group of the formula :



(wherein

R⁷ is halogen, lower alkyl, nitro lower alkoxy, carbamoyl, carboxy, protected carboxy, lower alkoxy, amino, phenoxy or phenyl(lower)alkoxy,

R⁸ is hydrogen, halogen or lower alkyl,

R⁹ is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy, hydroxy(lower)alkyl, nitro, amino, lower alkanoylamino, hydroxyamino, lower alkylamino, lower alkanoyloxy(lower)alkanoylamino, morpholino(lower)alkanoylamino,

lower alkoxy(lower)alkanoylamino, pyrrolyl which may have 1 to 3 lower alkyl, hydroxy(lower)alkanoylamino,

di-lower alkylamino(lower)alkyl, protected carboxy(lower)alkoxy, lower alkylsulfonylamino, or di-lower alkoxy(lower)alkylamino(lower)alkanoylamino,

R¹⁰ is hydrogen, halogen, lower alkyl, nitro, lower alkoxy, benzoyl, cyclo(lower)alkyl or tri-halo(lower)alkyl),

Y is a group of the formula : -NHCO- and

ℓ is an integer of 1.

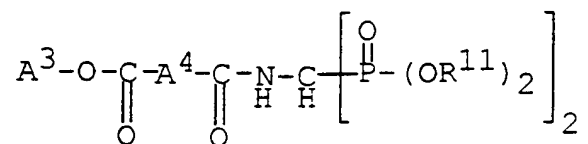
6. A compound of claim 5, wherein

R² is lower alkyl,

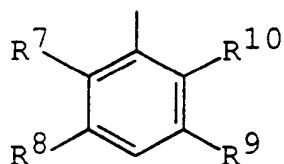
R³ is hydroxy(lower)alkyl, cyclo(lower)alkylaminocarbonyl-(lower)alkyl, protected carboxy(lower)alkyl, hydroxy(lower)alkylaminocarbonyl(lower)alkyl, lower

- 168 -

alkoxy(lower)alkylaminocarbonyl(lower)alkyl,
 carbonyl(lower)alkyl substituted with saturated 3 to 8-
 membered heteromonocyclic group containing 1 to 2 oxygen
 atom(s) and 1 to 3 nitrogen atom(s), lower
 5 alkylaminocarbonyl(lower)alkyl substituted with
 unsaturated 3 to 8-membered heteromonocyclic group
 containing 1 to 4 nitrogen atom(s),
 or a group of the formula :



(wherein A^3 is lower alkylene,
 R^{11} is hydrogen and
 A^4 is lower alkylene), and
 20 Z is a group of the formula :

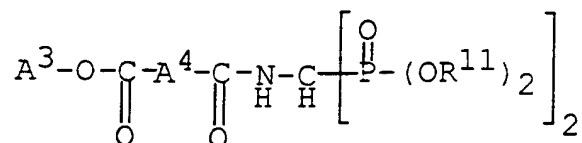


(wherein R^7 is halogen or lower alkyl,
 R^8 is hydrogen,
 R^9 is hydrogen, di-lower alkylamino(lower)-
 30 alkanoylamino, lower alkanoylamino, amino,
 lower alkoxy(lower)alkanoylamino,
 hydroxy(lower)alkancylamino, hydroxyamino,
 lower alkoxy or hydroxy, and
 R^{10} is halogen or lower alkyl).

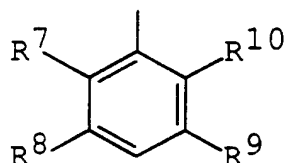
35

- 169 -

7. A compound of claim 6, wherein
 R^3 is hydroxy(lower)alkyl, or a group of the formula :

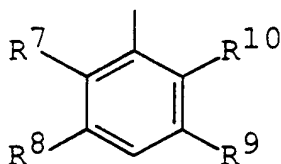


(wherein A^3 is lower alkylene,
 R^{11} is hydrogen, and
 A^4 is lower alkylene) and
 Z is a group of the formula :



(wherein R^7 is halogen or lower alkyl,
 R^8 and R^9 are each hydrogen, and
 R^{10} is halogen or lower alkyl).

8. A compound of claim 6, wherein
 R^3 is protected carboxy(lower)alkyl, and
 Z is a group of the formula :



(wherein R^7 is halogen or lower alkyl,

- 170 -

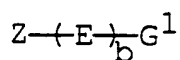
R^8 and R^9 are each hydrogen, and
 R^{10} is halogen or lower alkyl).

9. A compound of claim 6, wherein
 5 R^3 is cyclo(lower)alkylaminocarbonyl(lower)alkyl, and
 Z is a group of the formula :



(wherein R^7 is halogen or lower alkyl,
 R^8 and R^9 are each hydrogen, and
 15 R^{10} is halogen or lower alkyl).

10. A process for preparing a compound of claim 1,
 or a salt thereof,
 which comprises
 20 (i) reacting a compound of the formula :



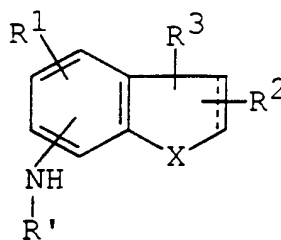
25 wherein Z is as defined in claim 1,
 E is lower alkylene, lower alkenylene,
 or a group of the formula :



(wherein G^1 is $-\text{COOH}$ or $-\text{SO}_3\text{H}$, and
 b is an integer of 0 or 1,),
 or its reactive derivative at the carboxy or sulfo group
 or a salt thereof, with a compound of the formula :

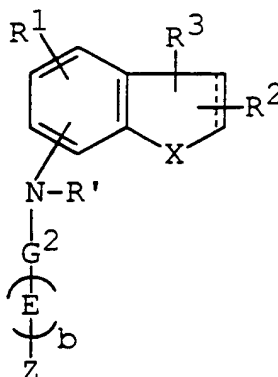
35

- 171 -



wherein

R^1 , R^2 , R^3 , ---- and X are each as defined in claim 1, and R' is hydrogen or lower alkyl, or its reactive derivative at the amino group or a salt thereof, to give a compound of the formula :



wherein R^1 , R^2 , R^3 , X, Z, R' , E, ---- and b are each as defined above, and

G^2 is $-CO-$ or $-SO_2-$, or a salt thereof, or

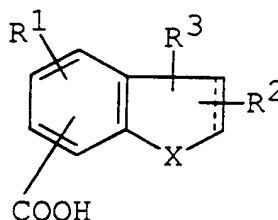
(ii) reacting a compound of the formula :



wherein Z is as defined in claim 1,

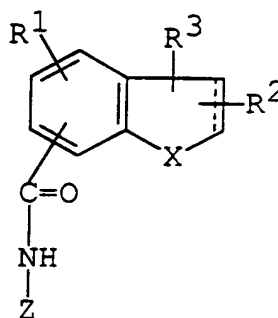
- 172 -

or its reactive derivative at the amino group or a salt thereof, with a compound of the formula :



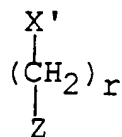
wherein R^1 , R^2 , R^3 , ---- and X are each as defined in claim 1,

or its reactive derivative at the carboxy group or a salt thereof, to give a compound of the formula :



wherein R^1 , R^2 , R^3 , X, ---- and Z are each as defined above, or a salt thereof, or

(iii) reacting a compound of the formula :



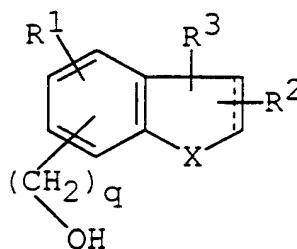
wherein Z is as defined in claim 1,

- 173 -

X' is halogen, and

r is an integer of 0 or 1,

or a salt thereof, with a compound of the formula :

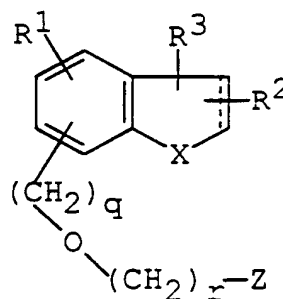


wherein R¹, R², R³, ---- and X are each as defined in
claim 1, and

q is an integer of 0 or 1,

or its reactive derivative at the hydroxy group,

or a salt thereof, to give a compound of the formula :

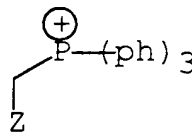


wherein R¹, R², R³, X, q, ---- and r are each as defined
above,

or a salt thereof, or

(iv) reacting a compound of the formula :

- 174 -



5 wherein Z is as defined in claim 1, or a salt thereof,
with a compound of the formula :



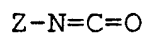
10
15 wherein R^1 , R^2 , R^3 , ---- and X are each as defined in
claim 1, and
 R'' is a leaving group,



20 or a salt thereof, to give a compound of the formula :

25
30 wherein R^1 , R^2 , R^3 , X, ---- and Z are each as defined above,
or a salt thereof, or

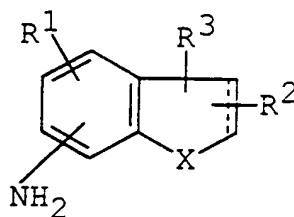
(v) reacting a compound of the formula :



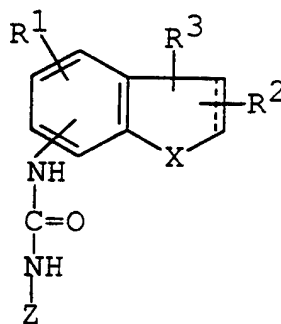
35

- 175 -

wherein Z is as defined in claim 1, or a salt thereof,
with a compound of the formula :

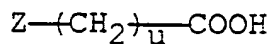


10 wherein R^1 , R^2 , R^3 , ---- and X are each as defined in
claim 1,
or its reactive derivative at the amino group,
or a salt thereof, to give a compound of the formula :



wherein R^1 , R^2 , R^3 , X, ---- and Z are each as defined above,
or a salt thereof, or

25 (vi) reacting a compound of the formula :

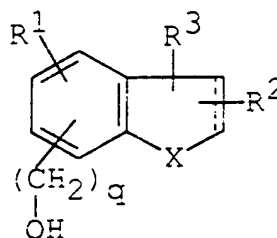


30 wherein Z is as defined in claim 1, and
u is an integer of 0 or 1,

or its reactive derivative at the carboxy group,
or a salt thereof, with a compound of the formula :

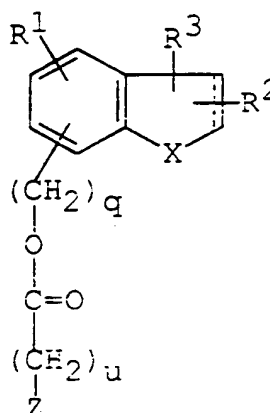
35

- 176 -



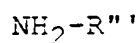
wherein R^1 , R^2 , R^3 , ---- and X are each as defined in
claim 1, and
q is defined above,

or a salt thereof, to give a compound of the formula :



wherein R^1 , R^2 , R^3 , X, Z, q, ---- and u are each as defined
above,
or a salt thereof, or

(Vii) reacting a compound of the formula :

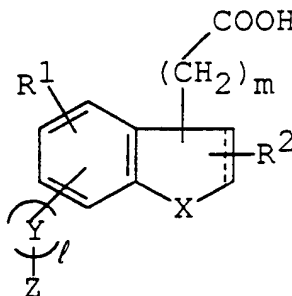


wherein

R'' is lower alkyl, cyclo(lower)alkyl, lower alkyl
substituted with heterocyclic group which may have one
or more suitable substituents, lower alkoxy(lower)alkyl,
hydroxy(lower)alkyl, amino, heterocyclic group,

- 177 -

carboxy(lower)alkyl, protected carboxy(lower)alkyl,
lower alkyl substituted with aryl which may have one or
more suitable substituent(s), arylsulfonyl, or its
reactive derivative at the amino group or a salt
thereof, with a compound of the formula :



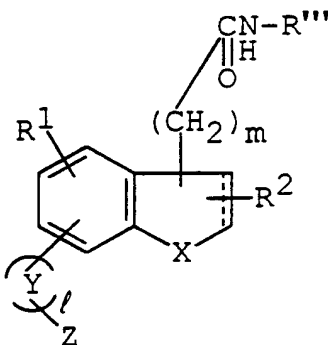
wherein

R^1 , R^2 , X, Y, Z, ---- and l are each as defined in claim 1,
and

m is an integer of 0 to 6,

or its reactive derivative at the carboxy group,

or a salt thereof, to give a compound of the formula :

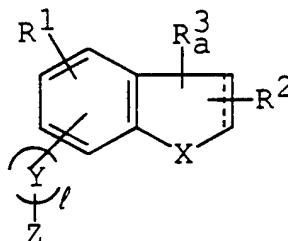


wherein R^1 , R^2 , R''' , X, Y, Z, l , ---- and m are each as
defined above,

or a salt thereof, or

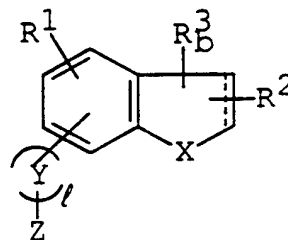
(Viii) reacting a compound of the formula :

- 178 -



wherein R^1 , R^2 , X, Y, Z, ---- and l are each as defined in claim 1, and

R_a^3 is lower alkyl substituted with oxo,
or a salt thereof, with Grignard reagent to give a compound
of the formula :

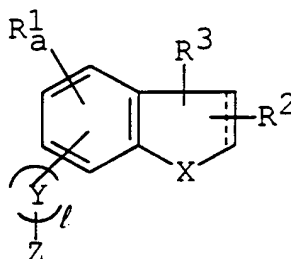


wherein R^1 , R^2 , X, Y, Z, ---- and l are each as defined above, and

R_b^3 is hydroxy(lower)alkyl,
or a salt thereof, or

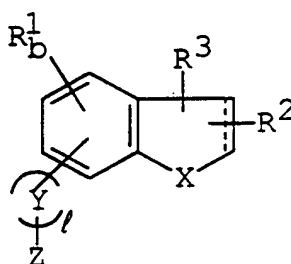
(ix) subjecting a compound of the formula :

- 179 -



5
10 wherein R^2 , R^3 , X, Y, Z, ---- and l are each as defined in claim 1, and

R^1_a is acylamino, or a salt thereof,
to de-acylation reaction of acyl group,
to give a compound of the formula :



15
20 wherein R^2 , R^3 , X, Y, Z, ---- and l are each as defined above, and

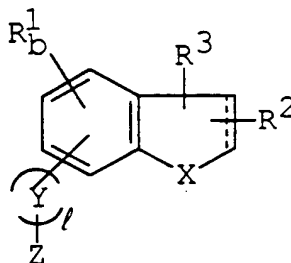
25 R^1_b is amino, or a salt thereof, or

(x) subjecting a compound of the formula :

30

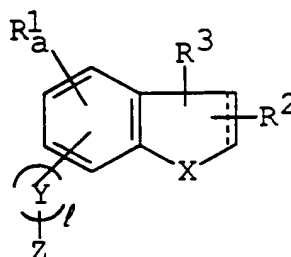
35

- 180 -



10 wherein R^2 , R^3 , X, Y, Z, ---- and l are each as defined in claim 1, and

R^1_b is amino, or a salt thereof,
to acylation of amino group, to give a compound of the
formula :



20 wherein R^2 , R^3 , X, Y, Z, ---- and l are each as defined
above, and

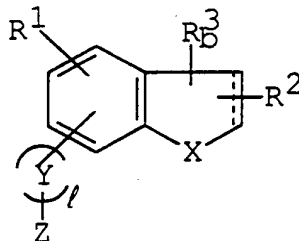
25 R^1_a is acylamino, or a salt thereof, or

(xi) subjecting a compound of the formula :

30

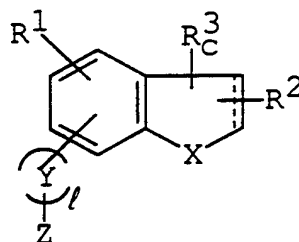
35

- 181 -



wherein R^1 , R^2 , X, Y, Z, ---- and l are each as defined in claim 1, and

R_B^3 is hydroxy(lower)alkyl,
or a salt thereof, to acylation reaction of hydroxy group,
to give a compound of the formula :



wherein R^1 , R^2 , X, Y, Z, ---- and l are each as defined above, and

R_C^3 is acyloxy(lower)alkyl,
or a salt thereof.

11. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

12. Use of a compound of claim 1 or a pharmaceutically

- 182 -

acceptable salt thereof for the manufacture of a
medicament.

5 13. A compound of claim 1 or a pharmaceutically acceptable
salt thereof for use as a medicament.

10 14. A method for the prophylactic and/or the therapeutic
treatment of diseases caused by abnormal bone metabolism
which comprises administering a compound of claim 1 or a
pharmaceutically acceptable salt thereof to a human
being or an animal.

15

20

25

30

35

INTERNATIONAL SEARCH REPORT

Inte onal Application No

PCT/JP 95/00787

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D307/79 C07D307/80 C07D307/81 C07D405/12 C07D413/12
 C07D409/12 C07D407/12 C07D495/04 A61K31/34
 //(C07D409/12, 333:00, 307:00), (C07D405/12, 307:00, 261:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | US-A-4 212 865 (RIKER) 15 July 1980 see the whole document --- | 1 |
| X | CHEMICAL ABSTRACTS, vol. 99, no. 19, 7 November 1983 Columbus, Ohio, US; abstract no. 158232f, see abstract & JP-A-58 103 380 (OTA SEIYAKU) --- | 1 |
| X | CHEMICAL ABSTRACTS, vol. 100, no. 15, 9 April 1984 Columbus, Ohio, US; abstract no. 120872r, page 574; see abstract & JP-A-58 170 775 (KAKEN SEIYAKU) --- -/-- | 1 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 August 1995

Date of mailing of the international search report

12.09.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+ 31-70) 340-3016

Authorized officer

Lauro, P

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 95/00787

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO-A-93 17013 (FUJISAWA) 2 September 1993 see claim 1 --- | 1 |
| X | EP-A-0 307 172 (ELI LILLY) 15 March 1989 see claim 1 --- | 1 |
| X | EP-A-0 516 257 (SCHERING) 2 December 1992 see claim 1 --- | 1 |
| A | EP-A-0 399 773 (MERCK) 28 November 1990 see the whole document --- | 1 |
| A | EP-A-0 547 545 (HOECHST) 23 June 1993 see page 3, line 5-14; claim 1 --- | 1 |
| A | EP-A-0 136 569 (TAKEDA) 10 April 1985 see page 1 & JP-A-06 054 379 cited in the application ----- | 1 1 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 95/00787

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-14 have been searched incompletely

Please see attached sheet ./.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/JP 95/00787

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The number of theoretically conceivable compounds resulting from the combination of all claimed substituents precludes a comprehensive search (Article 17 2(a)(ii) PCT).

Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application, the search has been limited to the group of compounds wherein $l=1$.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 95/00787

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|---|--|
| US-A-4212865 | 15-07-80 | NONE | |
| WO-A-9317013 | 02-09-93 | EP-A- 0626956 JP-T- 7504411 | 07-12-94 18-05-95 |
| EP-A-307172 | 15-03-89 | AU-A- 2191688 AU-B- 638790 AU-A- 6995391 CA-A- 1294281 EG-A- 19065 JP-A- 1110684 SU-A- 1777602 US-A- 5364863 | 09-03-89 08-07-93 18-04-91 14-01-92 30-11-94 27-04-89 23-11-92 15-11-94 |
| EP-A-516257 | 02-12-92 | DE-A- 4117512 AU-A- 1887092 CA-A- 2110062 WO-A- 9221669 HU-A- 65680 NO-A- 934248 | 26-11-92 08-01-93 10-12-92 10-12-92 28-07-94 24-11-93 |
| EP-A-399773 | 28-11-90 | US-A- 5006549 CA-A- 2017248 JP-A- 3056473 | 09-04-91 24-11-90 12-03-91 |
| EP-A-547545 | 23-06-93 | JP-A- 5221860 AT-T- 114465 CA-A- 2085421 DE-D- 69200757 DE-T- 69200757 ES-T- 2066546 US-A- 5317029 | 31-08-93 15-12-94 17-06-93 12-01-95 11-05-95 01-03-95 31-05-94 |
| EP-A-136569 | 10-04-85 | JP-A- 60054379 | 28-03-85 |